QUINAZOLINONES AND DERIVATIVES THEREOF AS FACTOR XA INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

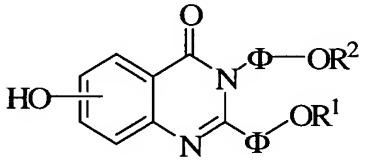
[0001] The present application claims the priority benefit of U.S. Provisional Application No. 60/420,098, filed October 21, 2002, which is expressly incorporated fully herein by reference.

FIELD OF THE INVENTION

[0002] This invention relates generally to quinazolinone compounds, which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

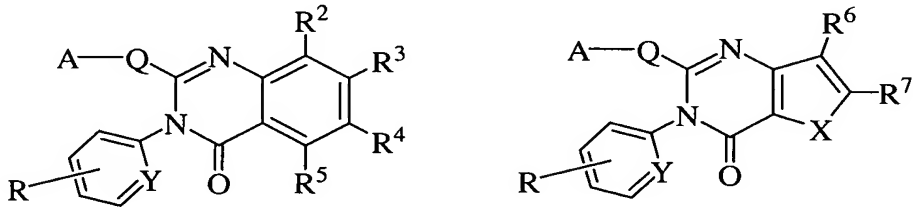
BACKGROUND OF THE INVENTION

[0003] US 5,948,775 illustrates partial estrogen agonists of the following formula:



wherein one of R^1 or R^2 is generally $(CH_2)_{2\text{-}3}NR^3R^4$. Inhibition of factor Xa is not considered. Compounds specifically described in US 5,948,775 are not considered to be part of the present invention.

[0004] WO02/26718 depicts factor Xa of the following formulae:



wherein A is a specifically listed nitrogen-containing group; Q is phenyl, pyridyl, furan, or thiophene; X is O or S; and Y is carbon or nitrogen. Compounds specifically described in WO02/26718 are not considered to be part of the present invention.

[0005] WO01/19798 describes factor Xa inhibitors of the following formula:

A-Q-D-E-G-J-X

wherein A, D, G, and X can be phenyl or heterocycle. However, none of the presently claimed compounds are exemplified or suggested in WO01/19798.

[0006] Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, S., Varadi, K.: Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation. *Thromb. Res.* **1979**, *15*, 617-629), inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

[0007] Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors. In addition, it is also desirable to find new compounds with improved pharmacological characteristics compared with known factor Xa inhibitors. For example, it is preferred to find new compounds with improved factor Xa inhibitory activity and selectivity for factor Xa versus other serine proteases (i.e., trypsin). It is also desirable and preferable to find compounds with advantageous and improved characteristics in one or more of the following categories, but are not limited to: (a) pharmaceutical properties (e.g., solubility, permeability, and amenability to sustained release formulations); (b) dosage requirements (e.g., lower dosages and/or once-daily dosing); (c) factors which decrease blood concentration peak-to-trough characteristics (e.g., clearance and/or volume of distribution); (d) factors that increase the concentration of active drug at the receptor (e.g., protein binding, volume of distribution); (e) factors that decrease the liability for clinical drug-drug interactions (e.g., cytochrome P450 enzyme inhibition or induction); (f) factors that decrease the potential for adverse side-effects (e.g., pharmacological selectivity beyond serine proteases, potential chemical or metabolic reactivity, and limited CNS penetration); and, (g) factors that improve manufacturing

costs or feasibility (e.g., difficulty of synthesis, number of chiral centers, chemical stability, and ease of handling).

SUMMARY OF THE INVENTION

[0008] Accordingly, the present invention provides novel quinazolinone compounds that are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

[0009] The present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

[0010] The present invention provides a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

[0011] The present invention provides a novel method of treating a patient in need of thromboembolic disorder treatment, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt thereof in an amount effective to treat a thromboembolic disorder.

[0012] The present invention provides a novel method, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt thereof in an amount effective to treat a thromboembolic disorder.

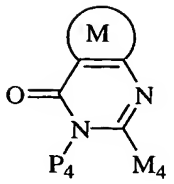
[0013] The present invention provides novel compounds for use in therapy.

[0014] The present invention provides the use of novel compounds for the manufacture of a medicament for the treatment of a thromboembolic disorder.

[0015] These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that the presently claimed quinazolinone compounds, or pharmaceutically acceptable salt or prodrug forms thereof, are effective factor Xa inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0016] In a first embodiment, the present invention provides a novel compound of formula I:



I

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

[0017] ring M is a 5 or 6 membered aromatic or dihydro-aromatic ring consisting of: carbon atoms and 0-3 heteroatoms selected from O, $S(O)_p$, and N;

[0018] ring M is substituted with 0-3 R^{1a} and 0-1 carbonyl groups;

[0019] one of P_4 and M_4 is -Z-A-B and the other $-G_1$-G;

[0020] G is a group of formula IIa or IIb:

IIa IIb

[0021] ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0022] ring D is substituted with 0-2 R and has 0-3 ring double bonds;

[0023] E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 1-2 R;

[0024] alternatively, ring D is absent and ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thienyl, and thiazolyl, and ring E is substituted with 1-2 R;

[0025] alternatively, ring D is absent and ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, triazolyl, thienyl, and thiazolyl, and ring E is substituted with 1 R and with a 5-6 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, wherein the heterocycle is substituted with 0-1 carbonyls, 1-2 R, and 0-3 ring double bonds;

[0026] R is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCH_2CH_2CH_3$, CN, $-C(=NR^8)NR^7R^9$, $-NHC(=NR^8)NR^7R^9$, $-NR^8CH(=NR^7)$, NH_2, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, $-C(=NH)NH_2$, $-CH_2NH_2$,

$-CH_2NH(C_{1-3}$ alkyl), $-CH_2N(C_{1-3}$ alkyl)$_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2NH(C_{1-3}$ alkyl), $-CH_2CH_2N(C_{1-3}$ alkyl)$_2$, $-(CR^8R^9)_tC(O)H$, $-(CR^8R^9)_tC(O)R^{2c}$, $-(CR^8R^9)_tNR^7R^8$, $-(CR^8R^9)_tC(O)NR^7R^8$, $-(CR^8R^9)_tNR^7C(O)R^7$, $-(CR^8R^9)_tOR^3$, $-(CR^8R^9)_tS(O)_pNR^7R^8$, $-(CR^8R^9)_tNR^7S(O)_pR^7$, $-(CR^8R^9)_tSR^3$, $-(CR^8R^9)_tS(O)R^3$, $-(CR^8R^9)_tS(O)_2R^3$, and $-OCF_3$, provided that $S(O)_pR^7$ forms other than $S(O)_2H$ or S(O)H;

[0027] alternatively, when 2 R groups are attached to adjacent atoms, they combine to form methylenedioxy or ethylenedioxy;

[0028] A is selected from: C_{3-10} carbocycle substituted with 0-2 R^4, and 5-12 membered heterocycle substituted with 0-2 R^4 and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0029] B is selected from: Y, X-Y, $-(CH_2)_{0-2}C(O)NR^2R^{2a}$, $-(CH_2)_{0-2}NR^2R^{2a}$, $-C(=NR^2)NR^2R^{2a}$, and $-NR^2C(=NR^2)NR^2R^{2a}$, provided that Z and B are attached to different atoms on A;

[0030] X is selected from $-(CR^2R^{2a})_{1-4}$-, $-CR^2(CR^2R^{2b})(CH_2)_t$-, -C(O)-, $-C(=NR^{1b})$-, $-CR^2(NR^{1b}R^2)$-, $-CR^2(OR^2)$-, $-CR^2(SR^2)$-, $-C(O)CR^2R^{2a}$-, $-CR^2R^{2a}C(O)$, -S-, -S(O)-, $-S(O)_2$-, $-SCR^2R^{2a}$-, $-S(O)CR^2R^{2a}$-, $-S(O)_2CR^2R^{2a}$-, $-CR^2R^{2a}S$-, $-CR^2R^{2a}S(O)$-, $-CR^2R^{2a}S(O)_2$-, $-S(O)_2NR^2$-, $-NR^2S(O)_2$-, $-NR^2S(O)_2CR^2R^{2a}$-, $-CR^2R^{2a}S(O)_2NR^2$-, $-NR^2S(O)_2NR^2$-, $-C(O)NR^2$-, $-NR^2C(O)$-, $-C(O)NR^2CR^2R^{2a}$-, $-NR^2C(O)CR^2R^{2a}$-, $-CR^2R^{2a}C(O)NR^2$-, $-CR^2R^{2a}NR^2C(O)$-, $-NR^2C(O)O$-, $-OC(O)NR^2$-, $-NR^2C(O)NR^2$-, $-NR^2$-, $-NR^2CR^2R^{2a}$-, $-CR^2R^{2a}NR^2$-, O, $-CR^2R^{2a}O$-, and $-OCR^2R^{2a}$-;

[0031] Y is selected from: C_{3-10} carbocycle substituted with 0-2 R^{4a}, and 5-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-2 R^{4a};

[0032] G_1 is absent or is selected from $-(CR^3R^{3a})_{1-5}$-, $-(CR^3R^{3a})_{0-2}CR^3{=}CR^3(CR^3R^{3a})_{0-2}$-, $-(CR^3R^{3a})_{0-2}C{\equiv}C(CR^3R^{3a})_{0-2}$-, $-(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w$-, $-(CR^3R^{3a})_uC(O)O(CR^3R^{3a})_w$-, $-(CR^3R^{3a})_uOC(O)(CR^3R^{3a})_w$-, $-(CR^3R^{3a})_uO(CR^3R^{3a})_w$-, $-CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_w$-, $-(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w$-,

$-(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uOC(O)NR^{3b}(CR^3R^{3a})_w-$,
$-(CR^3R^{3a})_uNR^{3b}C(O)O(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uNR^{3b}C(O)NR^{3b}(CR^3R^{3a})_w-$,
$-(CR^3R^{3a})_uNR^{3b}C(S)NR^{3b}(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uS(CR^3R^{3a})_w-$,
$-(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w-$,
$-(CR^3R^{3a})_uS(O)NR^{3b}(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uNR^{3b}S(O)_2(CR^3R^{3a})_w-$,
$-(CR^3R^{3a})_uS(O)_2NR^{3b}(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uNR^{3b}S(O)_2NR^{3b}(CR^3R^{3a})_w-$,
$-(CR^3R^{3a})_uNR^{3e}(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uC(O)(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w-$,
$-(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w-$,
$-(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w-$,
$-(CR^3R^{3a})_uC(O)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w-$,
$-(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w-$,
$-(CR^3R^{3a})_uS(O)NR^{3b}C(O)(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uC(O)NR^{3b}S(O)_2(CR^3R^{3a})_w-$, and
$-(CR^3R^{3a})_uS(O)_2NR^{3b}C(O)NR^{3b}CR^3R^{3a})_w-$, wherein u + w total 0, 1, 2, 3, or 4,
provided that G_1 does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either
group to which it is attached;

[0033] Z is selected from a bond, $-(CR^3R^{3a})_{1-4}-$, $-(CR^3R^{3a})_qO(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qNR^{3b}(CR^3R^{3a})_{q1}-$, $-(CR^3R^{3a})_qC(O)(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qC(O)O(CR^3R^{3a})_{q1}-$, $-(CR^3R^{3a})_qOC(O)(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qC(O)NR^{3b}(CR^3R^{3a})_{q1}-$, $-(CR^3R^{3a})_qNR^{3b}C(O)(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qOC(O)O(CR^3R^{3a})_{q1}-$, $-(CR^3R^{3a})_qOC(O)NR^{3b}(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qNR^{3b}C(O)O(CR^3R^{3a})_{q1}-$, $-(CR^3R^{3a})_qNR^{3b}C(O)NR^{3b}(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qC(O)(CR^3R^{3a})_qC(O)(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qNR^{3b}(CR^3R^{3a})_qC(O)NR^{3b}(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qNR^{3b}C(O)(CR^3R^{3a})_qC(O)(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qC(O)(CR^3R^{3a})_qC(O)NR^{3b}(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qNR^{3b}C(O)(CR^3R^{3a})_qC(O)NR^{3b}(CR^3R^{3a})_{q1}-$, $-(CR^3R^{3a})_qS(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qS(O)(CR^3R^{3a})_{q1}-$, $-(CR^3R^{3a})_qS(O)_2(CR^3R^{3a})_{q1}-$,
$-(CR^3R^{3a})_qSO_2NR^{3b}(CR^3R^{3a})_{q1}-$, $-(CR^3R^{3a})_qNR^{3b}SO_2(CR^3R^{3a})_{q1}-$,

$-(CR^3R^{3a})_qS(O)NR^{3b}C(O)(CR^3R^{3a})_{q1}-$, $-(CR^3R^{3a})_qC(O)NR^{3b}S(O)_2(CR^3R^{3a})_{q1}-$, and $-(CR^3R^{3a})_qNR^{3b}SO_2NR^{3b}(CR^3R^{3a})_{q1}-$, wherein q + q1 total 0, 1, 2, 3, or 4, provided that Z does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

[0034] R^{1a}, at each occurrence, is selected from H, $-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-CR^3R^{1b}R^{1b}$, $-(CR^3R^{3a})_r-O-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-NR^2-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-S(O)_p-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-CO_2-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-C(O)NR^2-(CR^3R^{3a})_r-R^{1b}$, $-(CR^3R^{3a})_r-C(O)-(CR^3R^{3a})_r-R^{1b}$, $-C_{2-6}$ alkenylene-R^{1b}, $-C_{2-6}$ alkynylene-R^{1b}, and $-(CR^3R^{3a})_r-C(=NR^{1b})NR^3R^{1b}$, provided that R^{1a} forms other than an N-halo, N-S, O-O, or N-CN bond;

[0035] alternatively, when two R^{1a} groups are attached to adjacent atoms, together with the atoms to which they are attached, they form a 5-7 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^{4b} and 0-3 ring double bonds;

[0036] R^{1b} is selected from H, C_{1-3} alkyl, F, Cl, Br, I, CN, NO_2, CHO, $-(CF_2)_rCF_3$, $-(CR^3R^{3a})_rOR^2$, $-NR^2R^{2a}$, $-C(O)R^{2b}$, $-CO_2R^{2b}$, $-OC(O)R^2$, $-CH(CH_2OR^2)_2$, $-(CF_2)_rCO_2R^{2a}$, $-S(O)_pR^{2b}$, $-NR^2(CH_2)_rOR^2$, $-C(=NR^{2c})NR^2R^{2a}$, $-NR^2C(O)R^{2b}$, $-NR^2C(O)NR^2R^{2a}$, $-NR^2C(O)_2R^{2a}$, $-OC(O)NR^2R^{2a}$, $-C(O)NR^2R^{2a}$, $-C(O)NR^2(CH_2)_rOR^2$, $-SO_2NR^2R^{2a}$, $-NR^2SO_2R^2$, $-C(O)NR^2SO_2R^2$, C_{3-6} carbocycle substituted with 0-2 R^{4b}, and 5-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, provided that R^{1b} forms other than an O-O, N-halo, N-S, or N-CN bond and provided that $S(O)_pR^2$ forms other than $S(O)_2H$ or S(O)H;

[0037] R^2, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0038] R^{2a}, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0039] alternatively, R^2 and R^{2a}, together with the nitrogen atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated, or unsaturated ring substituted with 0-2 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0040] R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl substituted with 0-2 R^{4b}, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0041] R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, $-(CH_2)_r-C_{3-10}$ carbocycle substituted with 0-2 R^{4b}, and $-(CH_2)_r$-5-10 membered heterocycle substituted with 0-2 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0042] R^3, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, and phenyl;

[0043] R^{3a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, and phenyl;

[0044] R^{3b}, at each occurrence, is selected from H, C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, $-(C_{0-4}$ alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and $-(C_{0-4}$ alkyl)- 5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0045] R^{3c}, at each occurrence, is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, and phenyl;

[0046] R^{3d}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, C_{1-4} alkyl-phenyl, and $C(=O)R^{3c}$;

[0047] R^{3e}, is selected from H, $-S(O)_2NHR^3$, $-C(O)R^3$, $-C(O)NHR^3$, $-C(O)OR^{3f}$, $-S(O)R^{3f}$, $-S(O)_2R^{3f}$, C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, $-(C_{0-4}$ alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and $-(C_{0-4}$ alkyl)- 5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0048] R^{3f}, at each occurrence, is selected from: C_{1-6} alkyl substituted with 0-2 R^{1a}, C_{2-6} alkenyl substituted with 0-2 R^{1a}, C_{2-6} alkynyl substituted with 0-2 R^{1a}, $-(C_{0-4}$ alkyl)-5-10 membered carbocycle substituted with 0-3 R^{1a}, and $-(C_{0-4}$ alkyl)-5-10 membered heterocycle substituted with 0-3 R^{1a} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0049] R^4, at each occurrence, is selected from H, =O, $(CR^3R^{3a})_rOR^2$, F, Cl, Br, I, C_{1-4} alkyl, $-(CR^3R^{3a})_rCN$, $-(CR^3R^{3a})_rNO_2$, $-(CR^3R^{3a})_rNR^2R^{2a}$, $-(CR^3R^{3a})_rC(O)R^{2c}$, $-(CR^3R^{3a})_rNR^2C(O)R^{2b}$, $-(CR^3R^{3a})_rC(O)NR^2R^{2a}$, $-(CR^3R^{3a})_rNR^2C(O)NR^2R^{2a}$, $-(CR^3R^{3a})_rC(=NR^2)NR^2R^{2a}$, $-(CR^3R^{3a})_rC(=NS(O)_2R^{5a})NR^2R^{2a}$, $-(CR^3R^{3a})_rNHC(=NR^2)NR^2R^{2a}$, $-(CR^3R^{3a})_rC(O)NHC(=NR^2)NR^2R^{2a}$, $-(CR^3R^{3a})_rSO_2NR^2R^{2a}$, $-(CR^3R^{3a})_rNR^2SO_2NR^2R^{2a}$, $-(CR^3R^{3a})_rNR^2SO_2$-C_{1-4} alkyl, $-(CR^3R^{3a})_rNR^2SO_2R^{5a}$, $-(CR^3R^{3a})_rS(O)_pR^{5a}$, $-(CR^3R^{3a})_r(CF_2)_rCF_3$, $-NHCH_2R^{1b}$, $-OCH_2R^{1b}$, $-SCH_2R^{1b}$, $-N(CH_2)_2(CH_2)_tR^{1b}$, $-O(CH_2)_2(CH_2)_tR^{1b}$, $-S(CH_2)_2(CH_2)_tR^{1b}$, $-(CR^3R^{3a})_r$-5-6 membered carbocycle substituted with 0-1 R^5, and a $-(CR^3R^{3a})_r$-5-6 membered heterocycle substituted with 0-1 R^5 and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0050] R^{4a}, at each occurrence, is selected from H, =O, -$(CR^3R^{3a})_rOR^2$, -$(CR^3R^{3a})_r$-F, -$(CR^3R^{3a})_r$-Br, -$(CR^3R^{3a})_r$-Cl, -$(CR^3R^{3a})_r$I, C_{1-4} alkyl, -$(CR^3R^{3a})_r$-CN, -$(CR^3R^{3a})_rNO_2$, -$(CR^3R^{3a})_rNR^2R^{2a}$, -$(CR^3R^{3a})_rC(O)R^{2c}$, -$(CR^3R^{3a})_rNR^2C(O)R^{2b}$, -$(CR^3R^{3a})_rC(O)NR^2R^{2a}$, -$(CR^3R^{3a})_rN{=}CHOR^3$, -$(CR^3R^{3a})_rC(O)NH(CH_2)_2NR^2R^{2a}$, -$(CR^3R^{3a})_rNR^2C(O)NR^2R^{2a}$, -$(CR^3R^{3a})_rNR^2C(O)OR^2$, -$(CR^3R^{3a})_rC(=NR^2)NR^2R^{2a}$, -$(CR^3R^{3a})_rNHC(=NR^2)NR^2R^{2a}$, -$(CR^3R^{3a})_rSO_2NR^2R^{2a}$, -$(CR^3R^{3a})_rNR^2SO_2NR^2R^{2a}$, -$(CR^3R^{3a})_rNR^2SO_2$-$C_{1-4}$ alkyl, -$(CR^3R^{3a})_rC(O)NHSO_2$-C_{1-4} alkyl, -$(CR^3R^{3a})_rNR^2SO_2R^5$, -$(CR^3R^{3a})_rS(O)_pR^5$, -$(CR^3R^{3a})_r(CF_2)_rCF_3$, -$(CR^3R^{3a})_r$-3-10 membered carbocycle substituted with 0-1 R^5, and a -$(CR^3R^{3a})_r$-3-10 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-1 R^5;

[0051] R^{4b}, at each occurrence, is selected from H, =O, -$(CR^3R^{3a})_rOR^3$, -$(CR^3R^{3a})_r$F,-$(CR^3R^{3a})_r$Cl, -$(CR^3R^{3a})_r$Br, -$(CR^3R^{3a})_r$I, C_{1-4} alkyl, -$(CR^3R^{3a})_r$CN, -$(CR^3R^{3a})_rNO_2$, -$(CR^3R^{3a})_rNR^3R^{3a}$, -$(CR^3R^{3a})_rC(O)R^3$, -$(CR^3R^{3a})_rC(O)OR^{3c}$, -$(CR^3R^{3a})_rNR^3C(O)R^{3a}$, -$(CR^3R^{3a})_rC(O)NR^3R^{3a}$, -$(CR^3R^{3a})_rNR^3C(O)NR^3R^{3a}$, -$(CR^3R^{3a})_rC(=NR^3)NR^3R^{3a}$, -$(CR^3R^{3a})_rNR^3C(=NR^3)NR^3R^{3a}$, -$(CR^3R^{3a})_rSO_2NR^3R^{3a}$, -$(CR^3R^{3a})_rNR^3SO_2NR^3R^{3a}$, -$(CR^3R^{3a})_rNR^3SO_2$-$C_{1-4}$ alkyl, -$(CR^3R^{3a})_rNR^3SO_2CF_3$, -$(CR^3R^{3a})_rNR^3SO_2$-phenyl, -$(CR^3R^{3a})_rS(O)_pCF_3$, -$(CR^3R^{3a})_rS(O)_p$-$C_{1-4}$ alkyl, -$(CR^3R^{3a})_rS(O)_p$-phenyl, and -$(CR^3R^{3a})_r(CF_2)_rCF_3$;

[0052] R^5, at each occurrence, is selected from H, C_{1-6} alkyl, =O, -$(CH_2)_rOR^3$, F, Cl, Br, I, -CN, NO_2, -$(CH_2)_rNR^3R^{3a}$, -$(CH_2)_rC(O)R^3$, -$(CH_2)_rC(O)OR^{3c}$, -$NR^3C(O)R^{3a}$, -$C(O)NR^3R^{3a}$, -$NR^3C(O)NR^3R^{3a}$, -CH(=NOR^{3d}), -$C(=NR^3)NR^3R^{3a}$, -$NR^3C(=NR^3)NR^3R^{3a}$, -$SO_2NR^3R^{3a}$, -$NR^3SO_2NR^3R^{3a}$, -NR^3SO_2-C_{1-4} alkyl, -$NR^3SO_2CF_3$, -NR^3SO_2-phenyl, -$S(O)_pCF_3$, -$S(O)_p$-C_{1-4} alkyl, -$S(O)_p$-phenyl, -$(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

[0053] R^{5a}, at each occurrence, is selected from C_{1-6} alkyl, $-(CH_2)_rOR^3$, $-(CH_2)_rNR^3R^{3a}$, $-(CH_2)_rC(O)R^3$, $-(CH_2)_rC(O)OR^{3c}$, $-(CH_2)_rNR^3C(O)R^{3a}$, $-(CH_2)_rC(O)NR^3R^{3a}$, $-(CF_2)_rCF_3$, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6, provided that R^{5a} does not form a S-N or $S(O)_p$-C(O) bond;

[0054] R^6, at each occurrence, is selected from H, OH, $-(CH_2)_rOR^2$, Fl, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2, $-(CH_2)_rNR^2R^{2a}$, $-(CH_2)_rC(O)R^{2b}$, $-NR^2C(O)R^{2b}$, $-NR^2C(O)NR^2R^{2a}$, $-C(=NH)NH_2$, $-NHC(=NH)NH_2$, $-SO_2NR^2R^{2a}$, $-NR^2SO_2NR^2R^{2a}$, and $-NR^2SO_2C_{1-4}$ alkyl;

[0055] R^7, at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkyl-C(O)-, C_{1-6} alkyl-O-, $(CH_2)_n$-phenyl, C_{1-4} alkyl-OC(O)-, C_{6-10} aryl-O-, C_{6-10} aryl-OC(O)-, C_{6-10} aryl-CH_2-C(O)-, C_{1-4} alkyl-C(O)O-C_{1-4} alkyl-OC(O)-, C_{6-10} aryl-C(O)O-C_{1-4} alkyl-OC(O)-, C_{1-6} alkyl-NH_2-C(O)-, phenyl-NH_2-C(O)-, and phenyl C_{1-4} alkyl-C(O)-;

[0056] R^8, at each occurrence, is selected from H, C_{1-6} alkyl, and - $(CH_2)_n$-phenyl;

[0057] alternatively, R^7 and R^8, when attached to the same nitrogen, combine to form a 5-10 membered heterocyclic ring consisting of carbon atoms and 0-2 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0058] R^9, at each occurrence, is selected from H, C_{1-6} alkyl, and $-(CH_2)_n$-phenyl;

[0059] n, at each occurrence, is selected from 0, 1, 2, and 3;

[0060] p, at each occurrence, is selected from 0, 1, and 2;

[0061] r, at each occurrence, is selected from 0, 1, 2, 3, 4, 5, and 6; and

[0062] t, at each occurrence, is selected from 0, 1, 2, and 3;

[0063] provided that:

(a) when Z and G_1 are absent, A is phenyl or pyridyl, G is phenyl, pyridyl, or thienyl, at least one R is other than a substituted or unsubstituted group selected from amidino, guanidino, guanidine-methyl, iminoamino,

iminoamino-methyl, amino, amino-methyl, and pyridyl, then B is other than cycloalkyl, $(CH_2)_{0-2}C(O)NR^2R^{2a}$, or $(CH_2)_{0-2}NR^2R^{2a}$, wherein substituted includes being cyclized with an additional heteroatom being optionally present;

(b) when Z and G_1 are absent, G is phenyl or pyridyl, and A is phenyl, pyridyl, furanyl, or thienyl, then B is other than a substituted or unsubstituted group selected from amidino, guanidino, guanidine-methyl, iminoamino, iminoamino-methyl, amino, amino-methyl, aminosulfonyl-phenyl, and pyridyl, wherein substituted includes being cyclized with an additional heteroatom being optionally present; and

(c) when $G\text{-}G_1$ is hydroxy-phenyl or alkoxy-phenyl, then B is other than acyclic or cyclic-amino-alkoxy.

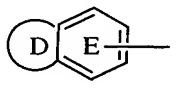
[0064] In a second embodiment, the present invention provides a novel compound, wherein:

[0065] ring M is selected from phenyl, pyrrole, furan, thiophene, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, 1,2,3-triazole, 1,2,3-oxadiazole, 1,2,3-thiadiazole, pyridine, pyrimidine, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, and 1,2,3,4-tetrazine;

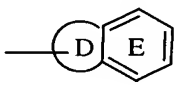
[0066] ring M is substituted with 0-3 R^{1a};

[0067] one of P_4 and M_4 is –Z-A-B and the other $-G_1$-G;

[0068] G is a group of formula IIa or IIb:



IIa



IIb

[0069] ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0070] ring D is substituted with 0-2 R and has 0-3 ring double bonds;

[0071] E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 1-2 R;

[0072] alternatively, ring D is absent, and ring E is selected from phenyl, pyridyl, pyrimidyl, and thienyl, and ring E is substituted with 1-2 R;

[0073] alternatively, ring D is absent, ring E is selected from phenyl, pyridyl, and thienyl, and ring E is substituted with a 5 membered heterocycle consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, wherein the heterocycle is substituted with 0-1 carbonyls, 1-2 R, and 0-3 ring double bonds;

[0074] R is selected from H, C_{1-4} alkyl, F, Cl, OH, OCH_3, $-OCH_2CH_3$, $-OCH(CH_3)_2$, CN, $-C(=NH)NH_2$, NH_2, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, $-C(=NH)NH_2$, $-CH_2NH_2$, $-CH_2NH(C_{1-3}$ alkyl), $-CH_2N(C_{1-3}$ alkyl)$_2$, $-(CR^8R^9)_tNR^7R^8$, $-C(O)NR^7R^8$, $-CH_2C(O)NR^7R^8$, $-S(O)_pNR^7R^8$, $-CH_2S(O)_pNR^7R^8$, and $-OCF_3$;

[0075] alternatively, when 2 R groups are attached to adjacent atoms, they combine to form methylenedioxy or ethylenedioxy;

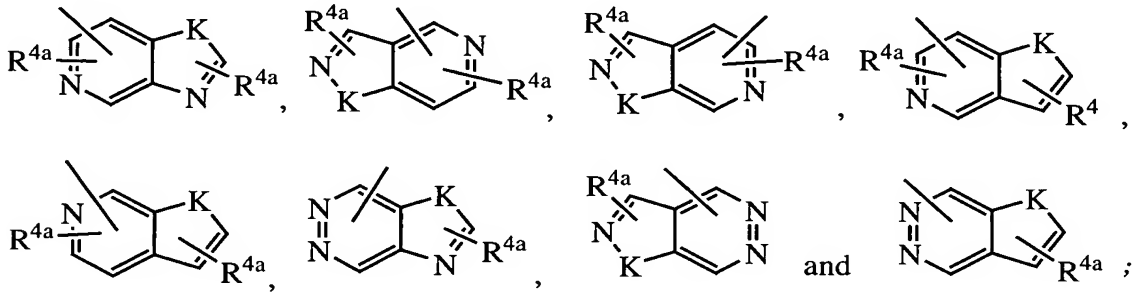
[0076] A is selected from one of the following rings and is substituted with 0-2 R^4; phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

[0077] B is selected from Y, X-Y, $-CH_2NR^2R^{2a}$, and $-CH_2CH_2NR^2R^{2a}$;

[0078] X is selected from $-(CR^2R^{2a})_{1-4}$-, -C(O)-, $-C(=NR^{1b})$-, $-CR^2(NR^{1b}R^2)$-, $-C(O)CR^2R^{2a}$-, $-CR^2R^{2a}C(O)$, $-C(O)NR^2$-, $-NR^2C(O)$-, $-C(O)NR^2CR^2R^{2a}$-, $-NR^2C(O)CR^2R^{2a}$-, $-CR^2R^{2a}C(O)NR^2$-, $-CR^2R^{2a}NR^2C(O)$-, $-NR^2C(O)NR^2$-, $-NR^2$-, $-NR^2CR^2R^{2a}$-, $-CR^2R^{2a}NR^2$-, O, $-CR^2R^{2a}O$-, and $-OCR^2R^{2a}$-;

[0079] Y is selected from one of the following rings and is substituted with 0-2 R^{4a}; cyclopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

[0080] alternatively, Y is selected from the following bicyclic heteroaryl ring systems:



[0081] K is selected from O, S, NH, and N;

[0082] G_1 is absent or is selected from $-(CR^3R^{3a})_{1-3}-$, $-(CR^3R^{3a})_uC(O)(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uO(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uNR^{3b}(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uNR^{3b}C(O)(CR^3R^{3a})_uC(O)NR^{3b}(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uS(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uS(O)(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uS(O)_2(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uS(O)NR^{3b}(CR^3R^{3a})_w-$, $-(CR^3R^{3a})_uNR^{3b}S(O)_2(CR^3R^{3a})_w-$, and $-(CR^3R^{3a})_uS(O)_2NR^{3b}(CR^3R^{3a})_w-$, wherein u + w total 0, 1, or 2, provided that G_1 does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

[0083] Z is selected from a bond, CH_2, CH_2CH_2, CH_2O, OCH_2, C(O), NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, C(O)NH, NHC(O), $NHC(O)CH_2C(O)NH$,

$S(O)_2$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

[0084] R^{1a}, at each occurrence, is selected from H, $-(CH_2)_r-R^{1b}$, $-(CH(CH_3))_r-R^{1b}$, $-(C(CH_3)_2)_r-R^{1b}$, $-O-(CR^3R^{3a})_r-R^{1b}$, $-NR^2-(CR^3R^{3a})_r-R^{1b}$, and $-S-(CR^3R^{3a})_r-R^{1b}$, provided that R^{1a} forms other than an N-halo, N-S, O-O, or N-CN bond;

[0085] alternatively, when two R^{1a} groups are attached to adjacent atoms, together with the atoms to which they are attached they form a 5-7 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^{4b} and 0-3 ring double bonds;

[0086] R^{1b} is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, F, Cl, Br, I, CN, CHO, CF_3, OR^2, $-NR^2R^{2a}$, $-C(O)R^{2b}$, $-CO_2R^{2b}$, $-OC(O)R^2$, $-CO_2R^{2a}$, $-S(O)_pR^{2b}$, $-NR^2(CH_2)_rOR^2$, $-NR^2C(O)R^{2b}$, $-NR^2C(O)NHR^2$, $-NR^2C(O)_2R^{2a}$, $-OC(O)NR^2R^{2a}$, $-C(O)NR^2R^{2a}$, $-C(O)NR^2(CH_2)_rOR^2$, $-SO_2NR^2R^{2a}$, $-NR^2SO_2R^2$, C_{5-6} carbocycle substituted with 0-2 R^{4b}, and 5-6 membered heterocycle substituted with 0-2 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, provided that R^{1b} forms other than an O-O, N-halo, N-S, or N-CN bond and provided that $S(O)_pR^2$ forms other than $S(O)_2H$ or S(O)H;

[0087] R^2, at each occurrence, is selected from H, CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{3-6} carbocycle substituted with 0-2 R^{4b}, C_{3-6} carbocycle-CH_2- substituted with 0-2 R^{4b}, and 5-6 membered heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0088] R^{2a}, at each occurrence, is selected from H, CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{5-6} carbocycle substituted with 0-2 R^{4b}, and 5-6 membered

heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0089] alternatively, R^2 and R^{2a}, together with the nitrogen atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated, or unsaturated ring substituted with 0-2 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0090] R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{5-6} carbocycle substituted with 0-2 R^{4b}, and 5-6 membered heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0091] R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, benzyl, C_{5-6} carbocycle substituted with 0-2 R^{4b}, and 5-6 membered heterocycle substituted with 0-2 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0092] R^3, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, and phenyl;

[0093] R^{3a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, and phenyl;

[0094] R^{3c}, at each occurrence, is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, and phenyl;

[0095] R^{3d}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2-phenyl, CH_2CH_2-phenyl, and $C(=O)R^{3c}$;

[0096] R^4, at each occurrence, is selected from H, =O, OR^2, $-CH_2OR^2$, $-(CH_2)_2OR^2$, F, Cl, Br, I, C_{1-4} alkyl, CN, NO_2, $-NR^2R^{2a}$, $-CH_2NR^2R^{2a}$, $-(CH_2)_2NR^2R^{2a}$, $-C(O)R^{2c}$, $-NR^2C(O)R^{2b}$, $-C(O)NR^2R^{2a}$, $-SO_2NR^2R^{2a}$, $-S(O)_pR^{5a}$, CF_3, CF_2CF_3, 5-6 membered carbocycle substituted with 0-1 R^5, and a 5-6 membered

heterocycle substituted with 0-1 R^5 and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[0097] R^{4a}, at each occurrence, is selected from H, =O, $-(CR^3R^{3a})_rOR^2$, $-(CR^3R^{3a})_r$-F, $-(CR^3R^{3a})_r$-Br, $-(CR^3R^{3a})_r$-Cl, C_{1-4} alkyl, $-(CR^3R^{3a})_r$-CN, $-(CR^3R^{3a})_rNO_2$, $-(CR^3R^{3a})_rNR^2R^{2a}$, $-(CR^3R^{3a})_rC(O)R^{2c}$, $-(CR^3R^{3a})_rNR^2C(O)R^{2b}$, $-(CR^3R^{3a})_rC(O)NR^2R^{2a}$, $-(CR^3R^{3a})_rSO_2NR^2R^{2a}$, $-(CR^3R^{3a})_rNR^2SO_2NR^2R^{2a}$, $-(CR^3R^{3a})_rNR^2SO_2$-C_{1-4} alkyl, $-(CR^3R^{3a})_rC(O)NHSO_2$-$C_{1-4}$ alkyl, $-(CR^3R^{3a})_rNR^2SO_2R^5$, $-(CR^3R^{3a})_rS(O)_pR^5$, $-(CR^3R^{3a})_r(CF_2)_rCF_3$, phenyl substituted with 0-1 R^5, and a 5 membered aromatic heterocycle consisting of: carbon atoms and 1-3 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

[0098] R^{4b}, at each occurrence, is selected from H, =O, OR^3, CH_2OR^3, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, CN, NO_2, $-NR^3R^{3a}$, $-CH_2NR^3R^{3a}$, $-C(O)R^3$, $-CH_2$-$C(O)R^3$, $-C(O)OR^{3c}$, $-CH_2C(O)OR^{3c}$, $-NR^3C(O)R^{3a}$, $-CH_2NR^3C(O)R^{3a}$, $-C(O)NR^3R^{3a}$, $-CH_2C(O)NR^3R^{3a}$, $-NR^3C(O)NR^3R^{3a}$, $-CH_2NR^3C(O)NR^3R^{3a}$, $-C(=NR^3)NR^3R^{3a}$, $-CH_2C(=NR^3)NR^3R^{3a}$, $-NR^3C(=NR^3)NR^3R^{3a}$, $-CH_2NR^3C(=NR^3)NR^3R^{3a}$, $-SO_2NR^3R^{3a}$, $-CH_2SO_2NR^3R^{3a}$, $-NR^3SO_2NR^3R^{3a}$, $-CH_2NR^3SO_2NR^3R^{3a}$, $-NR^3SO_2$-C_{1-4} alkyl, $-CH_2NR^3SO_2$-C_{1-4} alkyl, $-NR^3SO_2CF_3$, $-CH_2NR^3SO_2CF_3$, $-NR^3SO_2$-phenyl, $-CH_2NR^3SO_2$-phenyl, $-S(O)_pCF_3$, $-CH_2S(O)_pCF_3$, $-S(O)_p$-C_{1-4} alkyl, $-CH_2S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-CH_2S(O)_p$-phenyl, CF_3, and CH_2-CF_3;

[0099] R^5, at each occurrence, is selected from H, =O, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, OR^3, $-CH_2OR^3$, F, Cl, CN, NO_2, $-NR^3R^{3a}$, $-CH_2NR^3R^{3a}$, $-C(O)R^3$, $-CH_2C(O)R^3$, $-C(O)OR^{3c}$, $-CH_2C(O)OR^{3c}$, $-NR^3C(O)R^{3a}$, $-C(O)NR^3R^{3a}$, $-NR^3C(O)NR^3R^{3a}$, $-CH(=NOR^{3d})$, $-C(=NR^3)NR^3R^{3a}$, $-NR^3C(=NR^3)NR^3R^{3a}$, $-SO_2NR^3R^{3a}$, $-NR^3SO_2NR^3R^{3a}$, $-NR^3SO_2$-C_{1-4} alkyl, $-NR^3SO_2CF_3$,

$-NR^3SO_2$-phenyl, $-S(O)_pCF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, CF_3, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

[00100] R^6, at each occurrence, is selected from H, OH, OR^2, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, CN, NO_2, $-NR^2R^{2a}$, $-CH_2NR^2R^{2a}$, $-C(O)R^{2b}$, $-CH_2C(O)R^{2b}$, $-NR^2C(O)R^{2b}$, $-NR^2C(O)NR^2R^{2a}$, $-C(=NH)NH_2$, $-NHC(=NH)NH_2$, $-SO_2NR^2R^{2a}$, $-NR^2SO_2NR^2R^{2a}$, and $-NR^2SO_2C_{1-4}$ alkyl; and

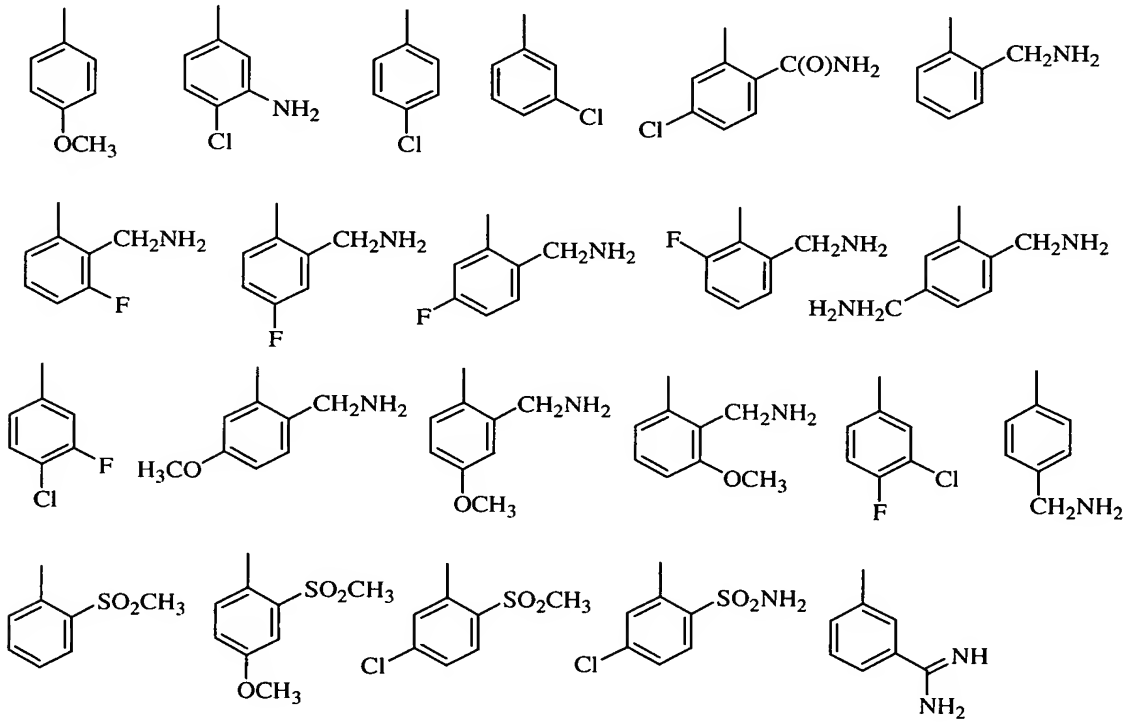
[00101] r, at each occurrence, is selected from 0, 1, 2, and 3.

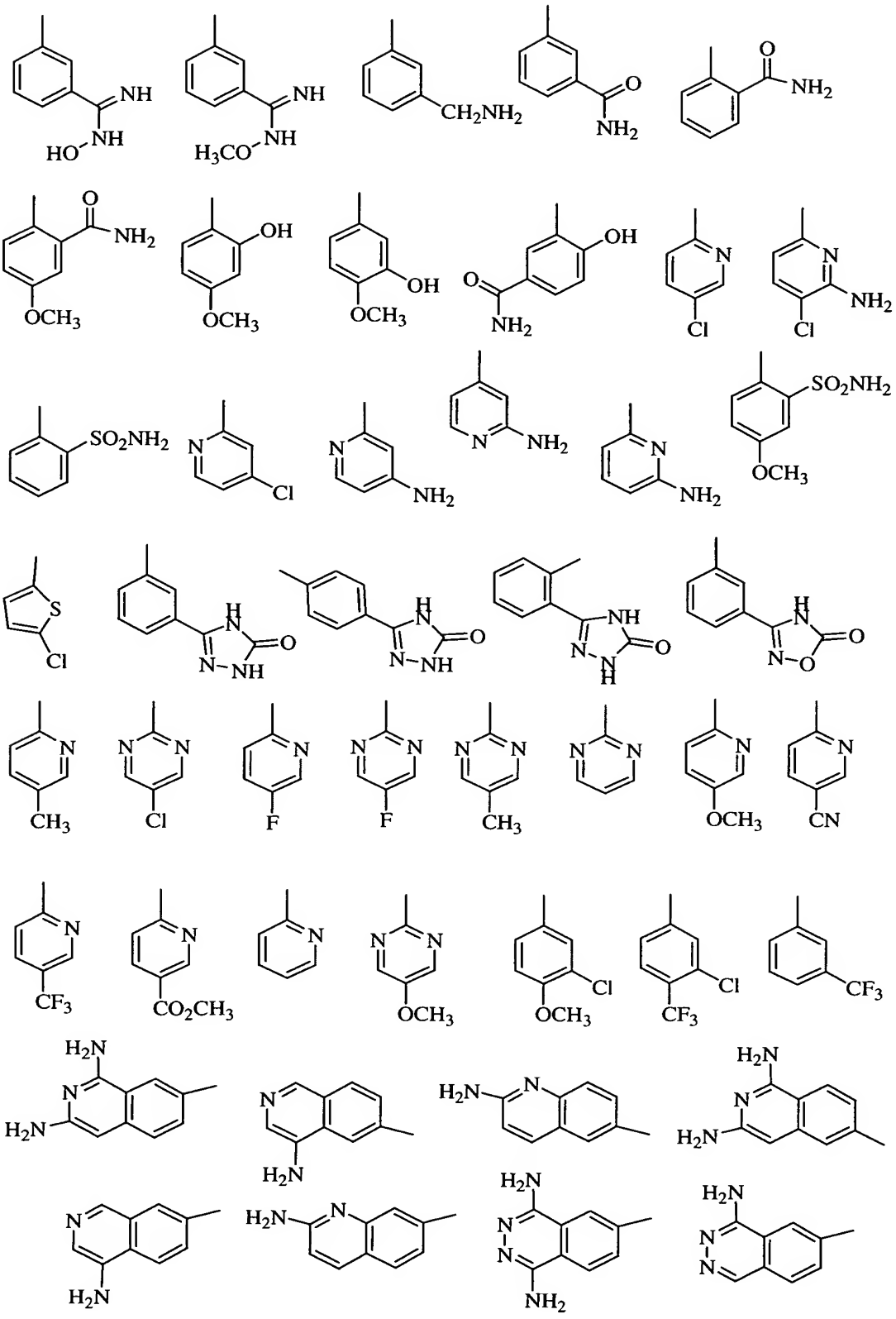
[00102] In a third embodiment, the present invention provides a novel compound, wherein:

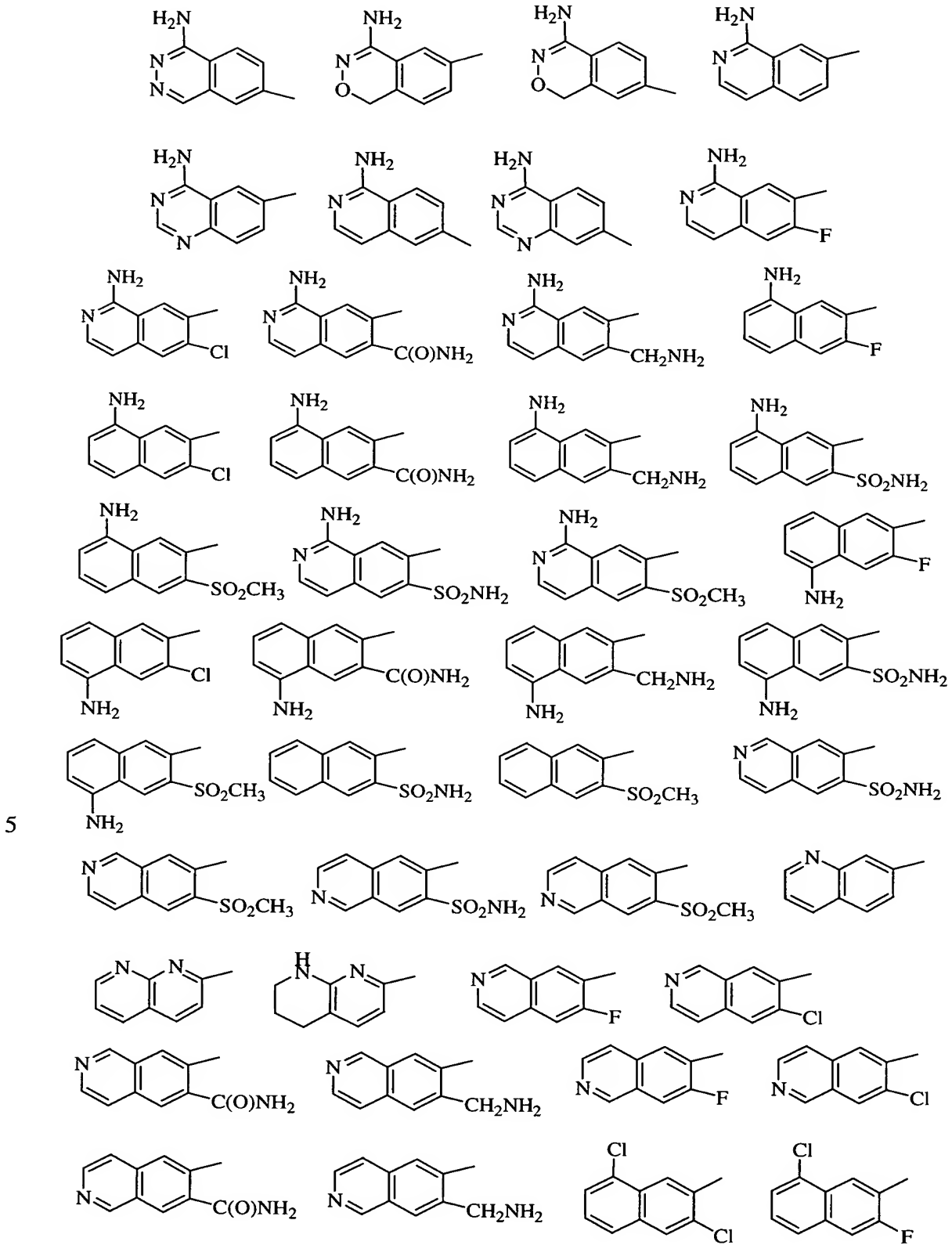
[00103] ring M is selected from phenyl, pyrrole, furan, thiophene, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, pyridine, and pyrimidine;

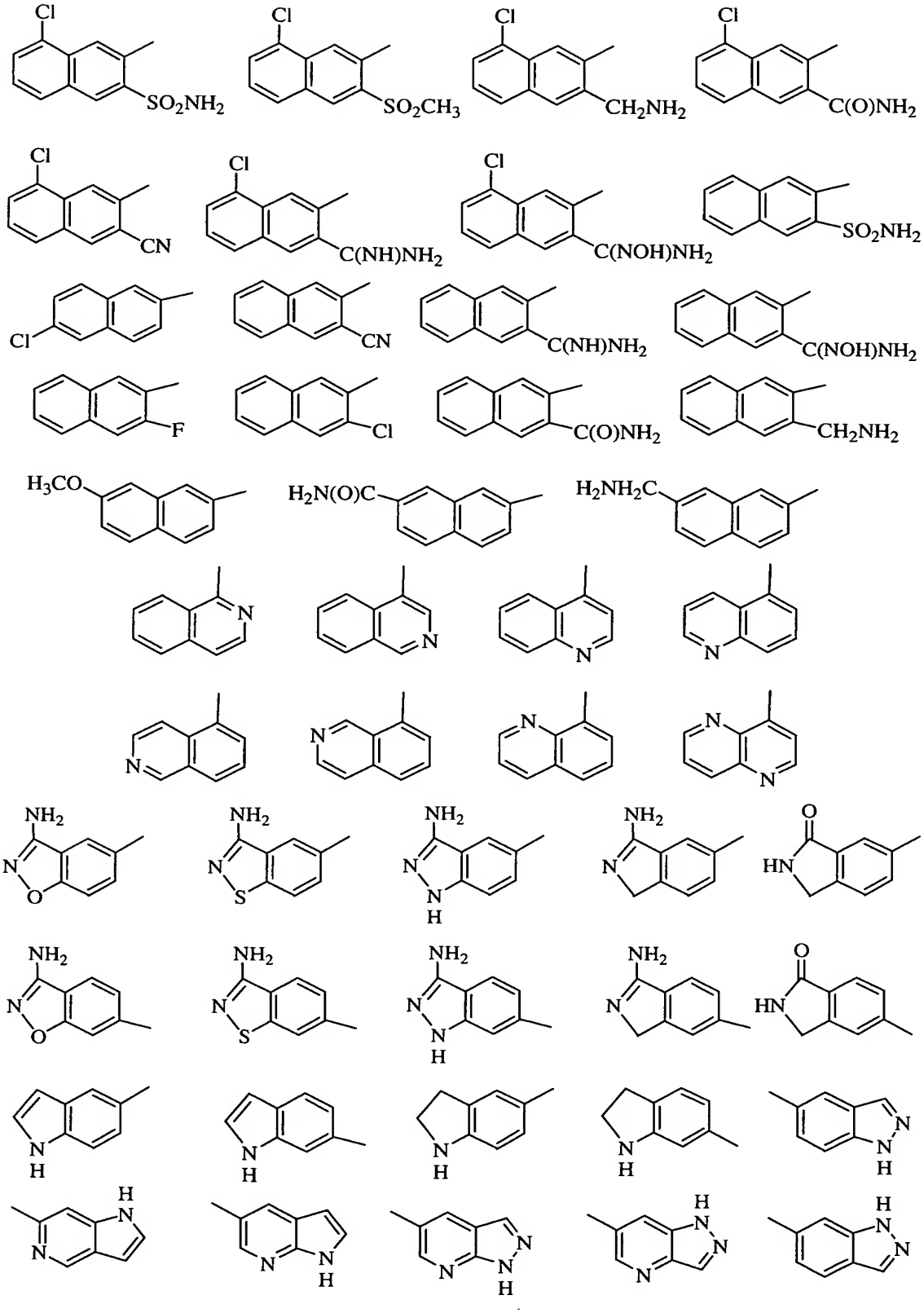
[00104] ring M is substituted with 0-2 R^{1a};

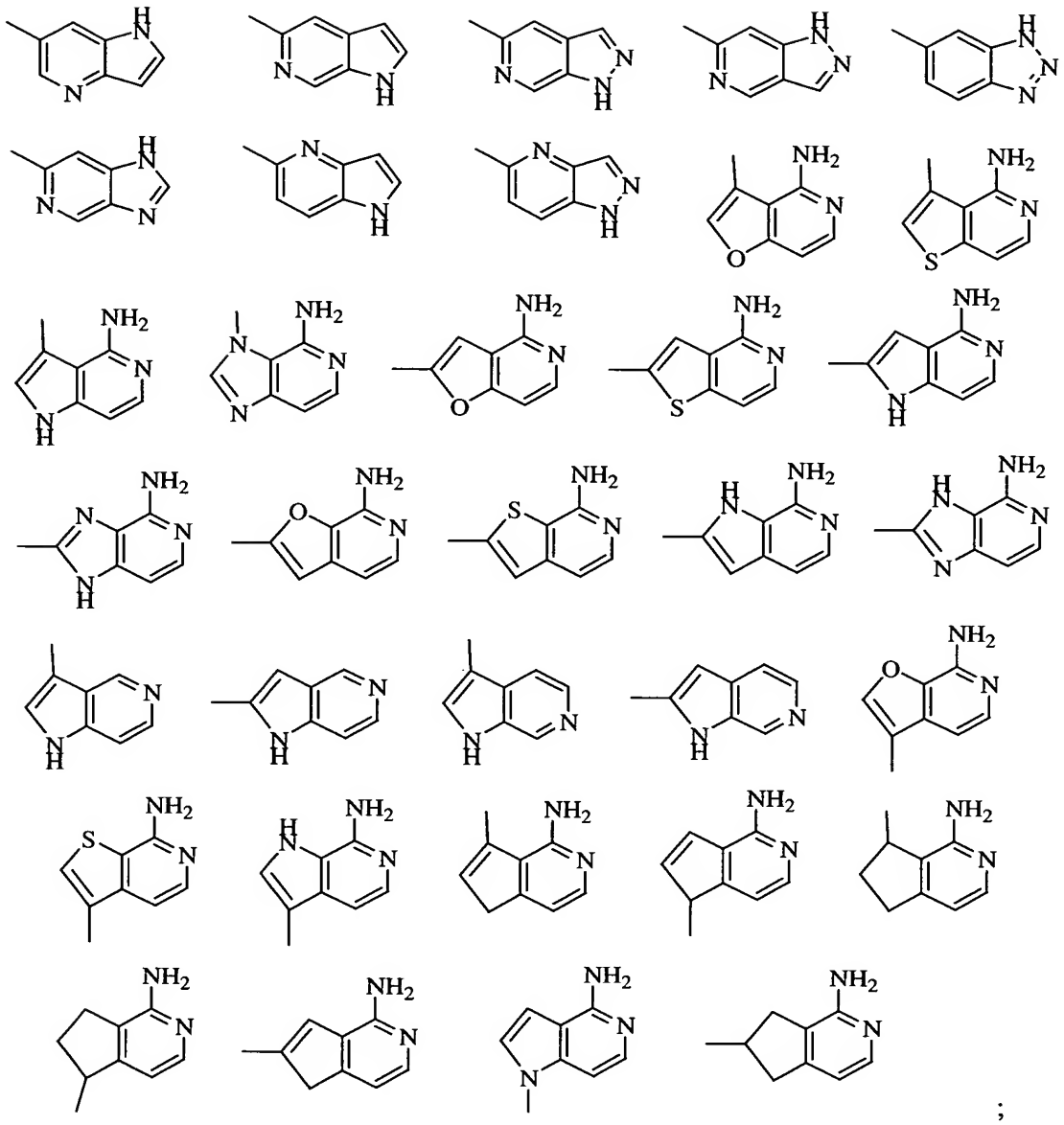
[00105] G is selected from the group:











;

[00106] R^{1a}, at each occurrence, is selected from H, R^{1b}, $-CH(CH_3)R^{1b}$, $-C(CH_3)_2R^{1b}$, $-CH_2R^{1b}$, and $-CH_2CH_2R^{1b}$, provided that R^{1a} forms other than an N-halo, N-S, or N-CN bond;

[00107] alternatively, when two R^{1a} groups are attached to adjacent atoms, together with the atoms to which they are attached, they form a 5-6 membered ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, this ring being substituted with 0-2 R^{4b} and 0-3 ring double bonds;

[00108] R^{1b} is selected from H, CH_3, CH_2CH_3, F, Cl, Br, CN, CHO, CF_3, OR^2, $-NR^2R^{2a}$, $-C(O)R^{2b}$, $-CO_2R^{2b}$, $-OC(O)R^2$, $-CO_2R^{2a}$, $-S(O)_pR^2$, $-NR^2(CH_2)_rOR^2$, $-NR^2C(O)R^{2b}$, $-C(O)NR^2R^{2a}$, $-SO_2NR^2R^{2a}$, $-NR^2SO_2R^2$, phenyl substituted with 0-2 R^{4b}, and 5-6 membered aromatic heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b}, provided that R^{1b} forms other than an O-O, N-halo, N-S, or N-CN bond;

[00109] R^2, at each occurrence, is selected from H, CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, phenyl substituted with 0-2 R^{4b}, a benzyl substituted with 0-2 R^{4b}, C_{3-6} cycloalkyl substituted with 0-2 R^{4b}, C_{3-6} cycloalkyl-CH_2- substituted with 0-2 R^{4b}, and 5-6 membered aromatic heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[00110] R^{2a}, at each occurrence, is selected from H, CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-2 R^{4b}, and 5-6 membered aromatic heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[00111] R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-2 R^{4b}, and 5-6 membered aromatic heterocycle substituted with 0-2 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[00112] R^{2c}, at each occurrence, is selected from CF_3, OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-2 R^{4b}, and 5-6 membered aromatic heterocycle substituted with 0-2 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[00113] alternatively, R^2 and R^{2a}, together with the nitrogen atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated, or unsaturated ring substituted with 0-2 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[00114] R^4, at each occurrence, is selected from H, $-(CH_2)_2OR^2$, $-CH_2OR^2$, OR^2, F, Cl, Br, I, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, CN, NO_2, $-NR^2R^{2a}$, $-CH_2NR^2R^{2a}$, $-(CH_2)_2NR^2R^{2a}$, $-C(O)R^{2c}$, $-NR^2C(O)R^{2b}$, $-C(O)NR^2R^{2a}$, $-SO_2NR^2R^{2a}$, CF_3, and CF_2CF_3;

[00115] R^{4a}, at each occurrence, is selected from H, =O, $-(CH_2)_rOR^2$, $-(CH_2)_r$-F, $-(CH_2)_r$-Br, $-(CH_2)_r$-Cl, C_{1-4} alkyl, $-(CH_2)_r$-CN, $-(CH_2)_rNO_2$, $-(CH_2)_rNR^2R^{2a}$, $-(CH_2)_rC(O)R^{2c}$, $-(CH_2)_rNR^2C(O)R^{2b}$, $-(CH_2)_rC(O)NR^2R^{2a}$, $-(CH_2)_rSO_2NR^2R^{2a}$, $-(CH_2)_rNR^2SO_2NR^2R^{2a}$, $-(CH_2)_rNR^2SO_2$-C_{1-4} alkyl, $-(CH_2)_rC(O)NHSO_2$-C_{1-4} alkyl, $-(CH_2)_rNR^2SO_2R^5$, $-(CH_2)_rS(O)_pR^5$, $-(CH_2)_r(CF_2)_rCF_3$, phenyl substituted with 0-1 R^5, and a 5 membered aromatic heterocycle consisting of: carbon atoms and 1-3 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-1 R^5;

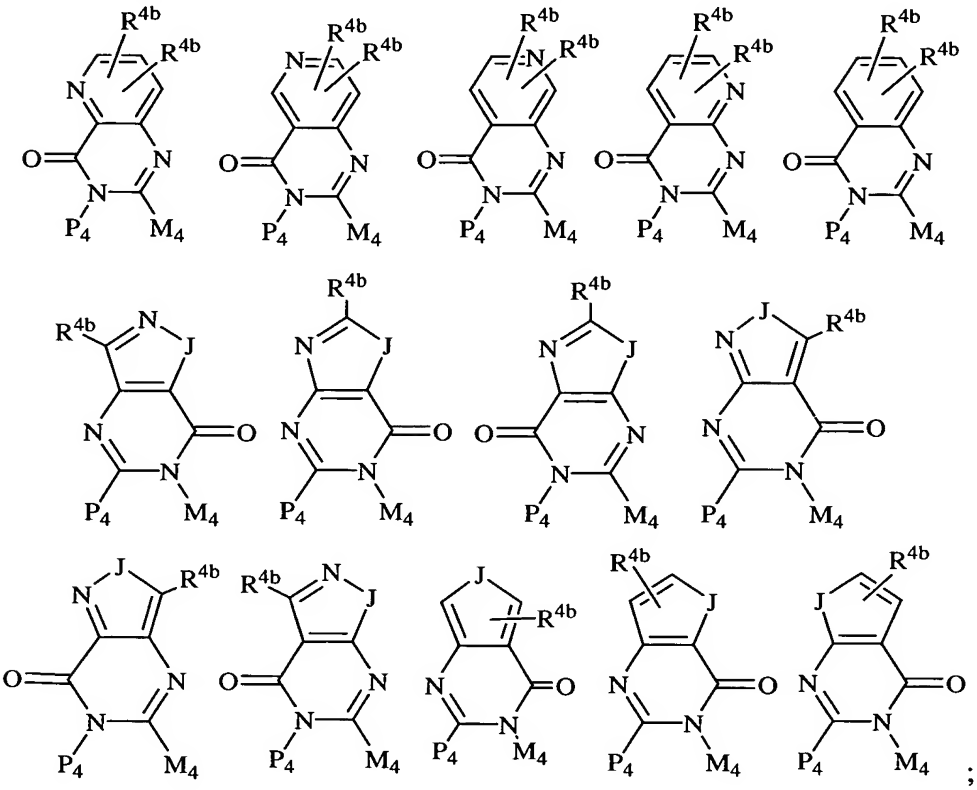
[00116] R^{4b}, at each occurrence, is selected from H, =O, OR^3, $-CH_2OR^3$, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CN, NO_2, $-NR^3R^{3a}$, $-CH_2NR^3R^{3a}$, $-C(O)R^3$, $-CH_2$-$C(O)R^3$, $-C(O)OR^{3c}$, $-CH_2$-$C(O)OR^{3c}$, $-NR^3C(O)R^{3a}$, $-CH_2NR^3C(O)R^{3a}$, $-C(O)NR^3R^{3a}$, $-CH_2$-$C(O)NR^3R^{3a}$, $-SO_2NR^3R^{3a}$, $-CH_2SO_2NR^3R^{3a}$, $-NR^3SO_2$-C_{1-4} alkyl, $-CH_2NR^3SO_2$-C_{1-4} alkyl, $-NR^3SO_2$-phenyl, $-CH_2NR^3SO_2$-phenyl, $-S(O)_pCF_3$, $-CH_2S(O)_pCF_3$, $-S(O)_p$-C_{1-4} alkyl, $-CH_2S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, $-CH_2S(O)_p$-phenyl, and CF_3;

[00117] R^5, at each occurrence, is selected from H, =O, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, OR^3, CH_2OR^3, F, Cl, CN, NO_2, $-NR^3R^{3a}$, $-CH_2NR^3R^{3a}$, $-C(O)R^3$, $-CH_2C(O)R^3$, $-C(O)OR^{3c}$, $-CH_2C(O)OR^{3c}$, $-NR^3C(O)R^{3a}$, $-C(O)NR^3R^{3a}$, $-SO_2NR^3R^{3a}$, $-NR^3SO_2$-C_{1-4} alkyl, $-NR^3SO_2CF_3$, $-NR^3SO_2$-phenyl, $-S(O)_pCF_3$, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, CF_3, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

[00118] R^6, at each occurrence, is selected from H, OH, OR^2, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CN, NO_2, $-NR^2R^{2a}$, $-CH_2NR^2R^{2a}$, $-C(O)R^{2b}$, $-CH_2C(O)R^{2b}$, $-NR^2C(O)R^{2b}$, $-SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl; and

[00119] r, at each occurrence, is selected from 0, 1, and 2.

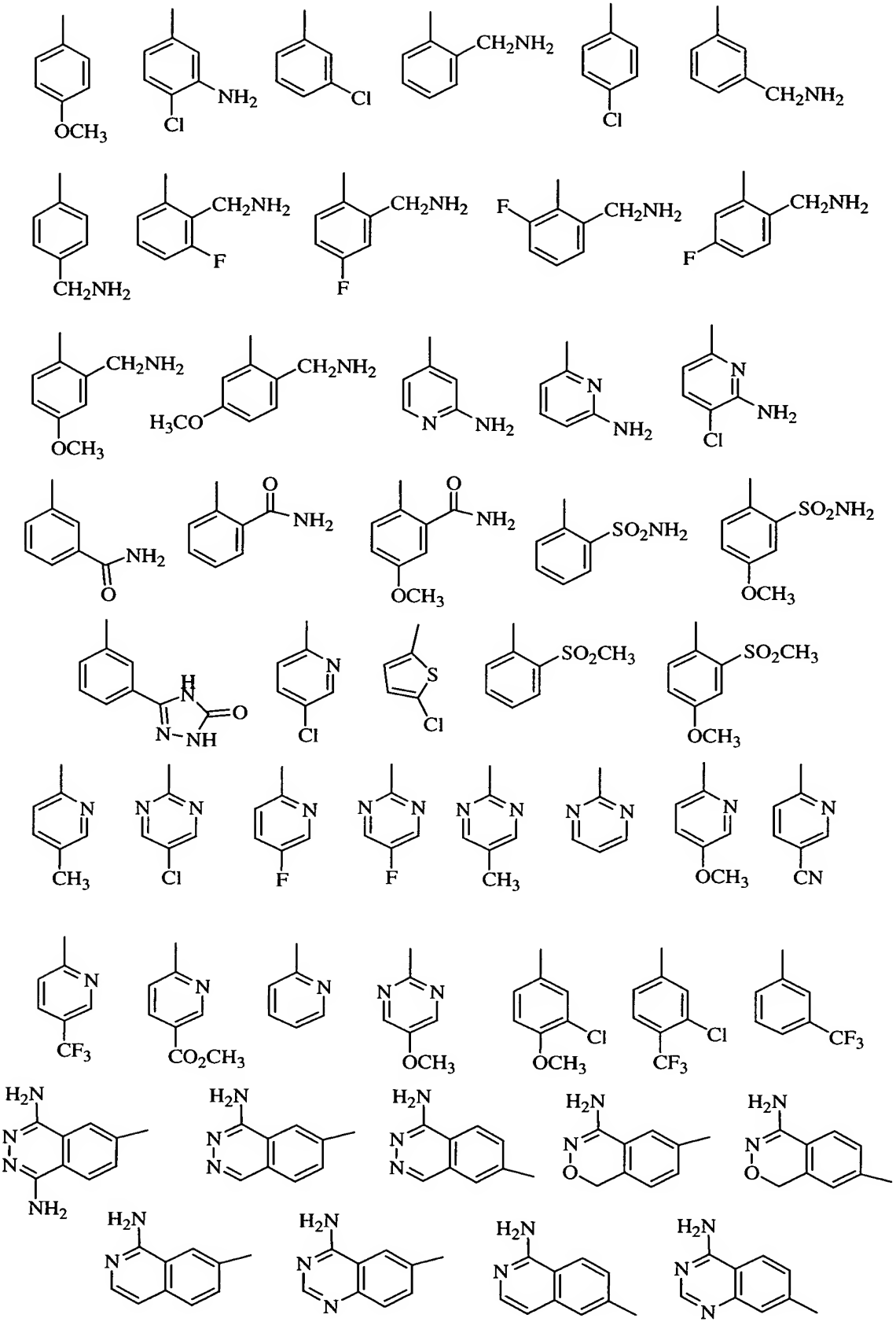
[00120] In a fourth embodiment, the present invention provides a novel compound, wherein the compound is selected from:

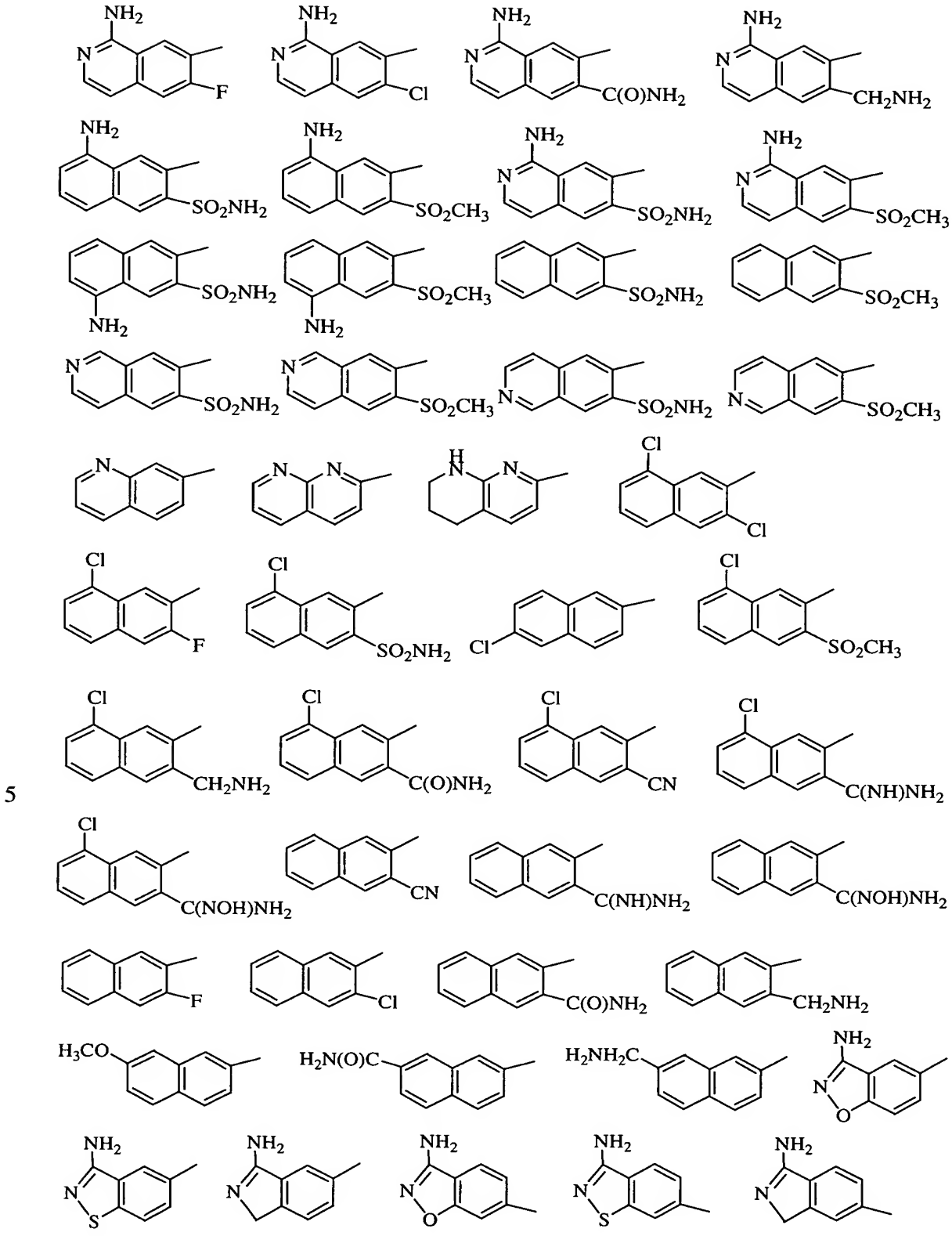


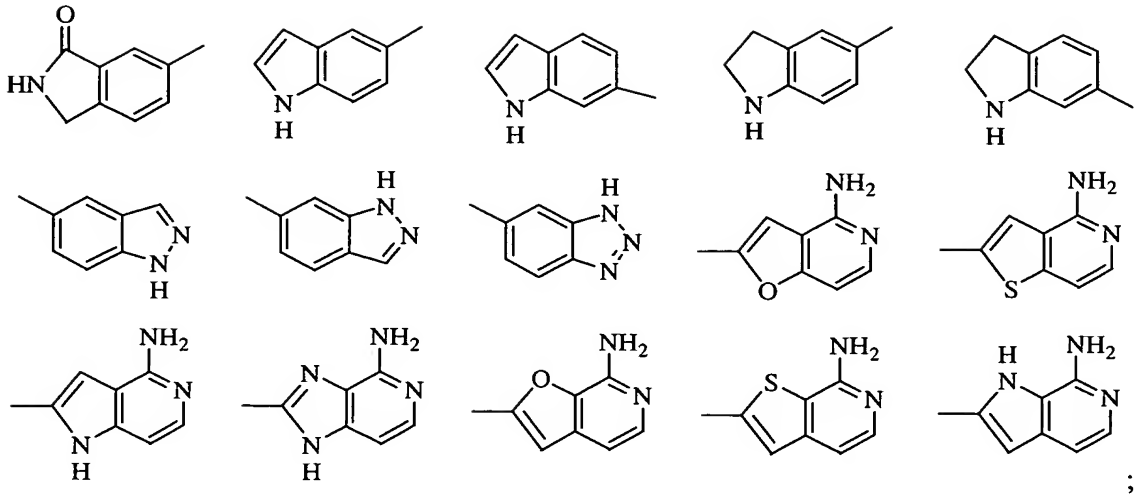
;

[00121] J is selected from O, S, NH, and NR^{1a};

[00122] G is selected from the group:







;

[00123] G_1 is absent or is selected from CH_2, CH_2CH_2, CH_2O, OCH_2, NH, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, C(O)NH, NHC(O), $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that G_1 does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

[00124] R^{1a}, at each occurrence, is selected from H, R^{1b}, $-CH(CH_3)R^{1b}$, $-C(CH_3)_2R^{1b}$, and $-CH_2R^{1b}$, provided that R^{1a} forms other than an N-halo, N-S, or N-CN bond;

[00125] R^{1b} is selected from CH_3, CH_2CH_3, F, Cl, Br, -CN, CF_3, OR^2, $-NR^2R^{2a}$, $-C(O)R^{2b}$, $-CO_2R^{2b}$, $-CO_2R^{2a}$, $-S(O)_pR^2$, $-C(O)NR^2R^{2a}$, $-SO_2NR^2R^{2a}$, $-NR^2SO_2R^2$, and 5-6 membered aromatic heterocycle consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{4b}, provided that R^{1b} forms other than an O-O, N-halo, N-S, or N-CN bond;

[00126] R^2, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, phenyl substituted with 0-1 R^{4b}, benzyl substituted with 0-1 R^{4b}, C_{3-5} cycloalkyl substituted with 0-1 R^{4b}, C_{3-5} cycloalkyl-CH_2- substituted with 0-1 R^{4b}, and 5-6 membered aromatic heterocycle substituted with 0-1 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[00127] R^{2a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-1 R^{4b}, and 5-6 membered aromatic heterocycle substituted with 0-1 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[00128] alternatively, R^2 and R^{2a}, together with the nitrogen atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated, or unsaturated ring substituted with 0-1 R^{4b} and consisting of: 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[00129] R^{2b}, at each occurrence, is selected from OCH_3, $-OCH_2CH_3$, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-1 R^{4b}, and 5-6 membered aromatic heterocycle substituted with 0-1 R^{4b} and consisting of: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[00130] R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, benzyl, phenyl substituted with 0-1 R^{4b}, and 5-6 membered aromatic heterocycle substituted with 0-1 R^{4b} and consisting of carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

[00131] R^4, at each occurrence, is selected from OH, OR^2, CH_2OR^2, $(CH_2)_2OR^2$, F, Br, Cl, I, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, $-NR^2R^{2a}$, $-CH_2NR^2R^{2a}$, $-(CH_2)_2NR^2R^{2a}$, CF_3, and CF_2CF_3;

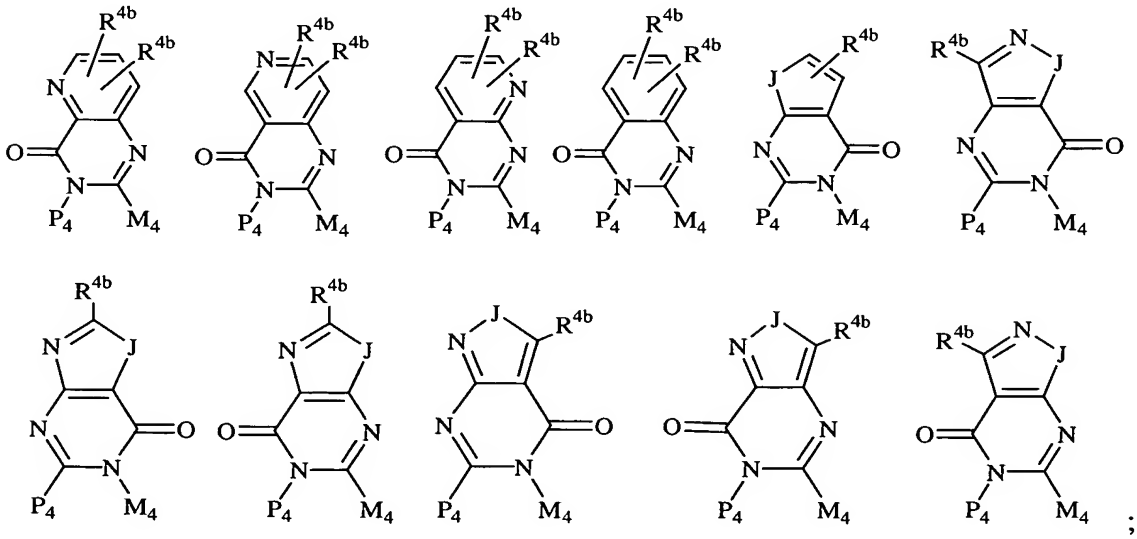
[00132] R^{4a}, at each occurrence, is selected from H, =O, $-(CH_2)_rOR^2$, F, Br, Cl, C_{1-4} alkyl, $-(CH_2)_rNR^2R^{2a}$, $-(CH_2)_rC(O)R^{2c}$, $-(CH_2)_rNR^2C(O)R^{2b}$, $-(CH_2)_rC(O)NR^2R^{2a}$, $-(CH_2)_rSO_2NR^2R^{2a}$, $-(CH_2)_rNR^2SO_2R^5$, $-(CH_2)_rS(O)_pR^5$, $-(CH_2)_r(CF_2)_rCF_3$, phenyl substituted with 0-1 R^5, and a 5 membered aromatic heterocycle consisting of: carbon atoms and 1-3 N and is substituted with 1 R^5;

[00133] R^{4b}, at each occurrence, is selected from H, =O, OR^3, $-CH_2OR^3$, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CN, NO_2, $-NR^3R^{3a}$, $-CH_2NR^3R^{3a}$, $-C(O)R^3$, $-C(O)OR^{3c}$, $-NR^3C(O)R^{3a}$, $-C(O)NR^3R^{3a}$, $-SO_2NR^3R^{3a}$, $-NR^3SO_2$-C_{1-4} alkyl, $-NR^3SO_2$-phenyl, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, and CF_3;

[00134] R^5, at each occurrence, is selected from H, =O, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, OR^3, CH_2OR^3, F, Cl, CN, NO_2, $-NR^3R^{3a}$, $-CH_2NR^3R^{3a}$, $-C(O)R^3$, $-C(O)OR^{3c}$, $-NR^3C(O)R^{3a}$, $-C(O)NR^3R^{3a}$, $-SO_2NR^3R^{3a}$, $-NR^3SO_2$-C_{1-4} alkyl, $-NR^3SO_2$-phenyl, $-S(O)_p$-C_{1-4} alkyl, $-S(O)_p$-phenyl, CF_3, phenyl substituted with 0-2 R^6, naphthyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6; and

[00135] R^6, at each occurrence, is selected from H, OH, OR^2, F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CN, NO_2, $-NR^2R^{2a}$, $-CH_2NR^2R^{2a}$, $-C(O)R^{2b}$, $-CH_2C(O)R^{2b}$, $-NR^2C(O)R^{2b}$, and $-SO_2NR^2R^{2a}$.

[00136] In a fifth embodiment, the present invention provides a novel compound, wherein the compound is selected from:



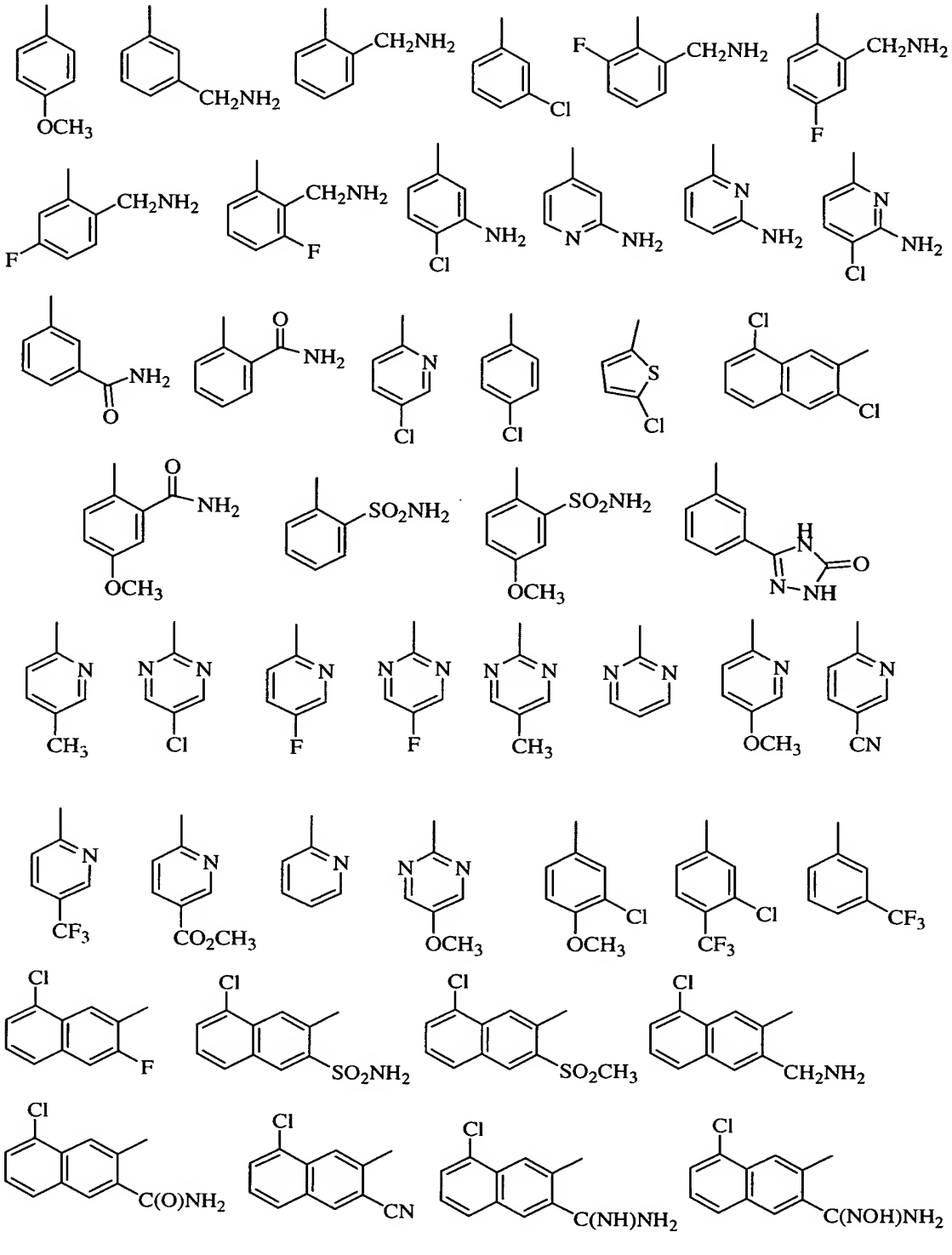
;

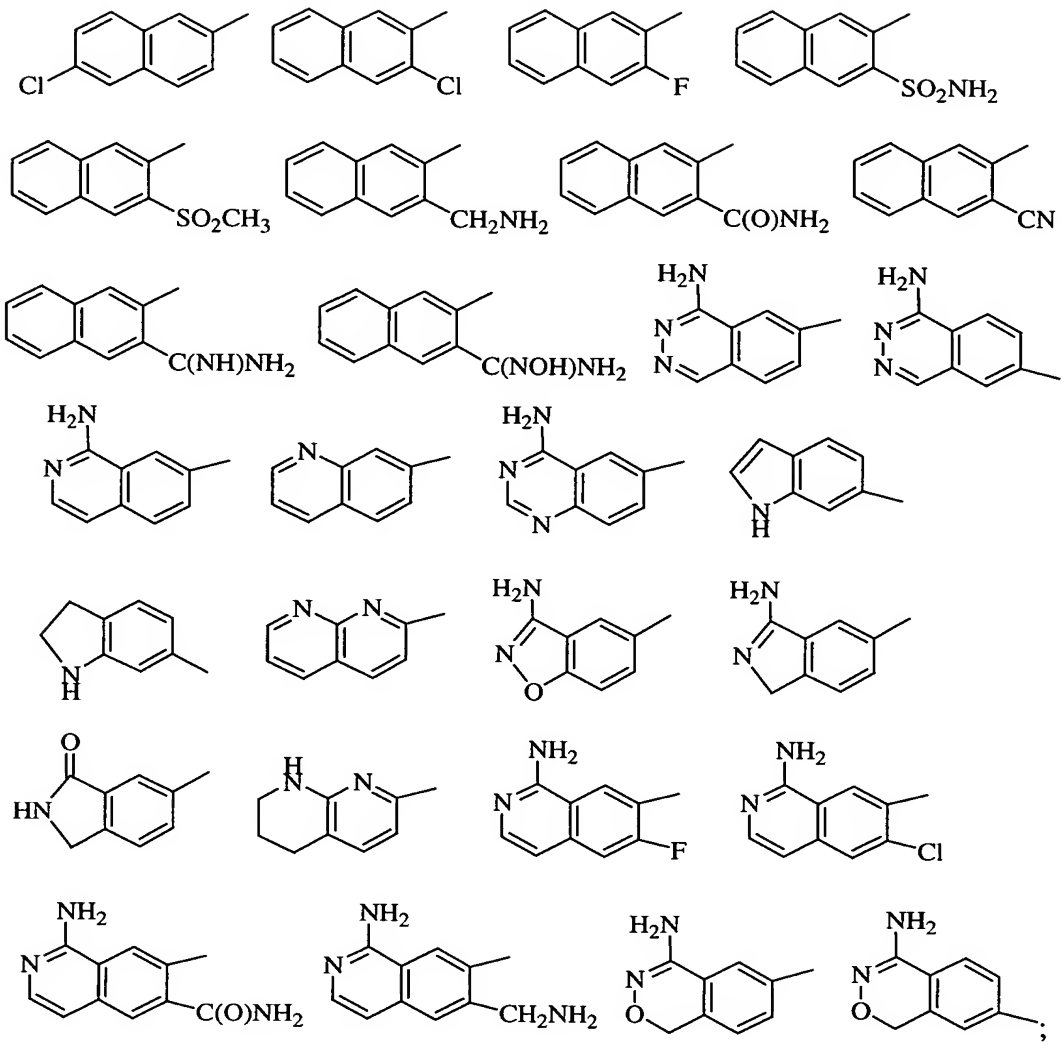
[00137] J is selected from O, S, NH, and NR^{1a};

[00138] P_4 is $-G_1$-G;

[00139] M_4 is –Z-A-B;

[00140] G is selected from:





[00141] G_1 is absent or is selected from CH_2CH_2, CH_2O, OCH_2, CH_2NH, $NHCH_2$, $CH_2C(O)$, $C(O)CH_2$, $C(O)NH$, $NHC(O)$, SO_2NH, and $NHSO_2$, provided that G_1 does not form a N-S, NCH_2N, NCH_2O, or NCH_2S bond with either group to which it is attached;

[00142] A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4;

[00143] B is selected from phenyl, pyrrolidinyl, N-pyrrolidino-carbonyl, morpholinyl, N-morpholino-carbonyl, 1,2,3-triazolyl, imidazolyl, and benzimidazolyl, and is substituted with 0-1 R^{4a};

[00144] R^{1a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, CH_2F, CH_2Cl, Br, CH_2Br, -CN, CH_2CN, CF_3, CH_2CF_3, OCH_3, CH_2OH, $C(CH_3)_2OH$, CH_2OCH_3, NH_2, CH_2NH_2, $NHCH_3$, CH_2NHCH_3, $N(CH_3)_2$, $CH_2N(CH_3)_2$, CO_2H, $COCH_3$, CO_2CH_3, $CH_2CO_2CH_3$, SCH_3, CH_2SCH_3, $S(O)CH_3$, $CH_2S(O)CH_3$, $S(O)_2CH_3$, $CH_2S(O)_2CH_3$, $C(O)NH_2$, $CH_2C(O)NH_2$, SO_2NH_2, $CH_2SO_2NH_2$, $NHSO_2CH_3$, $CH_2NHSO_2CH_3$, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2-yl-N-oxide, pyridin-3-yl-N-oxide, pyridin-4-yl-N-oxide, imidazol-1-yl, CH_2-imidazol-1-yl, 4-methyl-oxazol-2-yl, 4-N,N-dimethylaminomethyl-oxazol-2-yl, 1,2,3,4-tetrazol-1-yl, 1,2,3,4-tetrazol-5-yl, -CH_2-1,2,3,4-tetrazol-1-yl, and -CH_2-1,2,3,4-tetrazol-5-yl, provided that R^{1a} forms other than an N-halo, N-S, or N-CN bond;

[00145] R^2, at each occurrence, is selected from H, CH_3, CH_2CH_3, cyclopropylmethyl, cyclobutyl, and cyclopentyl;

[00146] R^{2a}, at each occurrence, is H or CH_3;

[00147] alternatively, R^2 and R^{2a}, together with the atom to which they are attached, combine to form pyrrolidine substituted with 0-2 R^{4b} or piperidine substituted with 0-2 R^{4b};

[00148] R^{2b}, at each occurrence, is selected from OCH_3, OCH_2CH_3, CH_3, and CH_2CH_3;

[00149] R^{2c}, at each occurrence, is selected from OH, OCH_3, OCH_2CH_3, CH_3, and CH_2CH_3;

[00150] R^4, at each occurrence, is selected from OH, OR^2, CH_2OR^2, $(CH_2)_2OR^2$, F, Br, Cl, I, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $C(CH_3)_3$, -NR^2R^{2a}, -$CH_2NR^2R^{2a}$, -$(CH_2)_2NR^2R^{2a}$, CF_3, and CF_2CF_3;

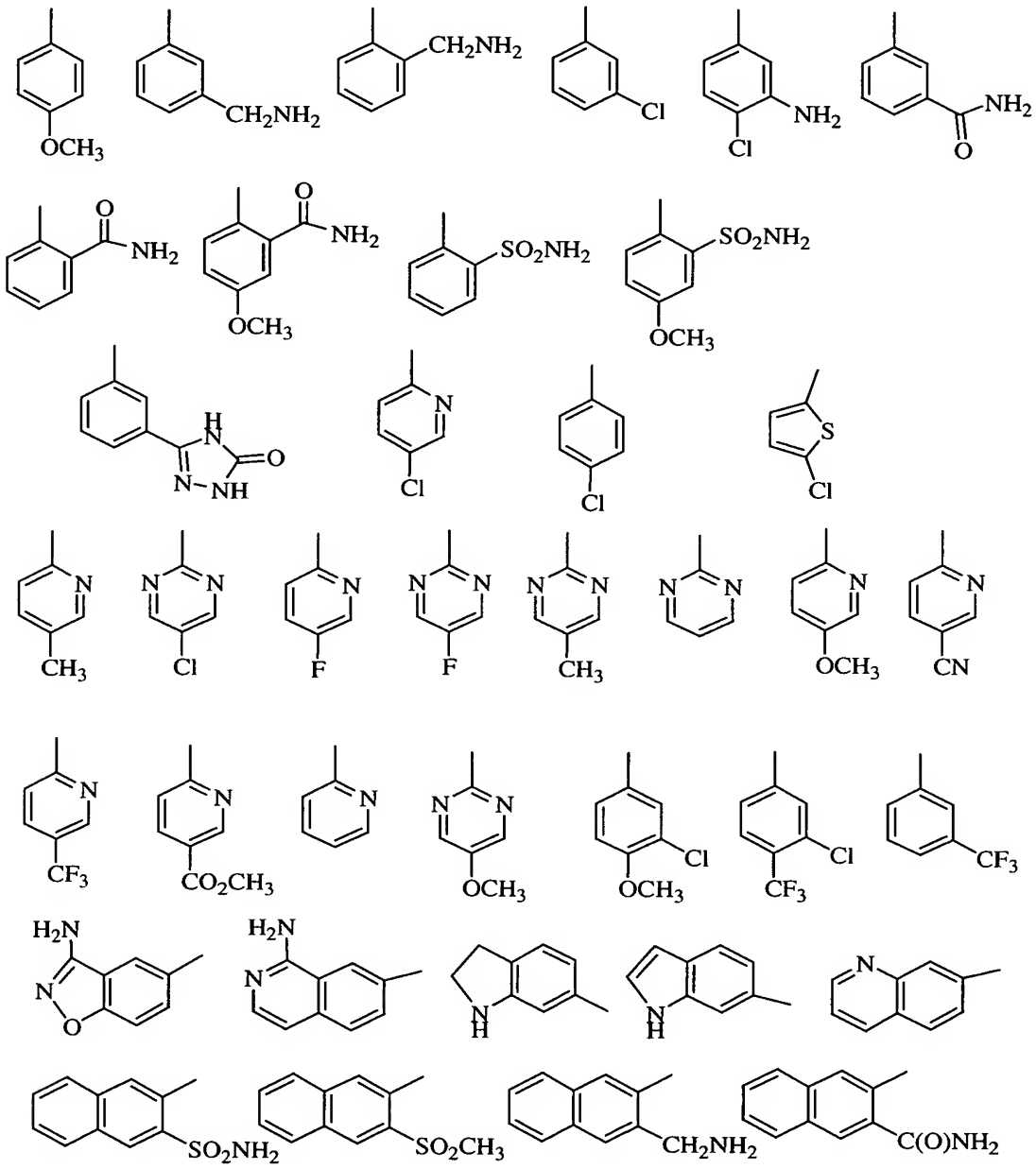
[00151] R^{4a} is selected from C_{1-4} alkyl, CF_3, OR^2, -CH_2OR^2, -$(CH_2)_2OR^2$, -NR^2R^{2a}, -$CH_2NR^2R^{2a}$, -$(CH_2)_2NR^2R^{2a}$, -$S(O)_pR^5$, -$SO_2NR^2R^{2a}$, and 1-CF_3-tetrazol-2-yl;

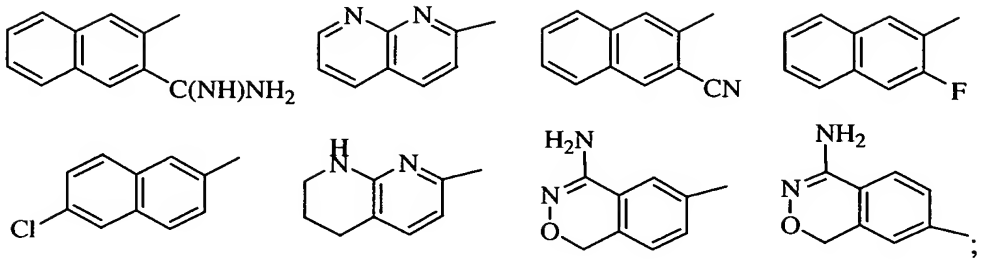
[00152] R^{4b}, at each occurrence, is selected from H, CH_3, and OH; and

[00153] R^5, at each occurrence, is selected from CF_3, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, phenyl, and benzyl.

[00154] In a sixth embodiment, the present invention provides a novel compound, wherein:

[00155] G is selected from:





[00156] A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and

[00157] B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, N-pyrrolidino-carbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(N-methylaminomethyl)phenyl, 2-(N-ethyl-N-methylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(dimethylaminomethyl)-1-imidazolyl, 2-(methylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-(cyclopentyl)aminomethyl)phenyl, 2-(N-(4-hydroxypiperidinyl)methyl)phenyl, and 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl.

[00158] In a seventh embodiment, the present invention provides a novel compound, wherein the compound is selected from the group:

2-biphenyl-4-yl-6-chloro-3-(4-chloro-phenyl)-3*H*-quinazolin-4-one;

6-chloro-3-(4-chloro-phenyl)-2-phenyl-3*H*-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-methyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-ethyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

2-{4-[1-(2-amino-ethyl)-1H-pyrrol-2-yl]-phenyl}-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-methylamino-ethyl)-1H-pyrrol-2-yl]-phenyl}-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-ethylamino-ethyl)-1H-pyrrol-2-yl]-phenyl}-3H-quinazolin-4-one;

2-{4-[1-(2-benzylamino-ethyl)-1H-pyrrol-2-yl]-phenyl}-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-pyridin-2-yl-2-[4-(1-{2-[(pyridin-2-ylmethyl)-amino]-ethyl}-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-pyridin-2-yl-2-[4-(1-{2-[(pyridin-3-ylmethyl)-amino]-ethyl}-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-pyridin-2-yl-2-[4-(1-{2-[(pyridin-4-ylmethyl)-amino]-ethyl}-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

2-[4-(1-benzyl-1H-pyrrol-2-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-pyridin-2-ylmethyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-pyridin-3-ylmethyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-pyridin-4-ylmethyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-cyclohexyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(tetrahydro-pyran-4-yl)-1H-pyrrol-2-yl]-phenyl}-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-piperidin-4-yl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(1-methyl-piperidin-4-yl)-1H-pyrrol-2-yl]-phenyl}-3H-quinazolin-4-one;

2-{4-[1-(1-acetyl-piperidin-4-yl)-1H-pyrrol-2-yl]-phenyl}-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-isopropyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-cyclopropyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-cyclobutyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-cyclopentyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(tetrahydro-furan-3-yl)-1H-pyrrol-2-yl]-phenyl}-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2',3',4',5'-tetrahydro-1'H-[1,3']bipyrrolyl-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1'-methyl-2',3',4',5'-tetrahydro-1'H-[1,3']bipyrrolyl-2-yl)-phenyl]-3H-quinazolin-4-one;

2-[4-(1'-acetyl-2',3',4',5'-tetrahydro-1'H-[1,3']bipyrrolyl-2-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1'-methanesulfonyl-2',3',4',5'-tetrahydro-1'H-[1,3']bipyrrolyl-2-yl)-phenyl]-3H-quinazolin-4-one;

N-[2-(2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-pyrrol-1-yl)-ethyl]-acetamide;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-hydroxy-ethyl)-1H-pyrrol-2-yl]-phenyl}-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-methoxy-ethyl)-1H-pyrrol-2-yl]-phenyl}-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-methoxy-1-methyl-ethyl)-1H-pyrrol-2-yl]-phenyl}-3H-quinazolin-4-one;

2-(2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-pyrrol-1-yl)-acetamide;

2-(2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-pyrrol-1-yl)-N-methyl-acetamide;

3-(5-chloro-pyridin-2-yl)-2-[4-(1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-methyl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-ethyl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

2-{4-[1-(2-amino-ethyl)-1H-imidazol-2-yl]-phenyl}-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-methylamino-ethyl)-1H-imidazol-2-yl]-phenyl}-3H-quinazolin-4-one;

2-{4-[1-(2-ethylamino-ethyl)-1H-imidazol-2-yl]-phenyl}-3-pyridin-2-yl-3H-quinazolin-4-one;

2-{4-[1-(2-benzylamino-ethyl)-1H-imidazol-2-yl]-phenyl}-3-pyridin-2-yl-3H-quinazolin-4-one;

3-pyridin-2-yl-2-[4-(1-{2-[(pyridin-2-ylmethyl)-amino]-ethyl}-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-pyridin-2-yl-2-[4-(1-{2-[(pyridin-3-ylmethyl)-amino]-ethyl}-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

2-{4-[1-(2-benzylamino-ethyl)-1H-imidazol-2-yl]-phenyl}-3-pyridin-2-yl-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-pyridin-2-ylmethyl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-pyridin-3-ylmethyl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-pyridin-4-ylmethyl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-cyclohexyl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(tetrahydro-pyran-4-yl)-1H-imidazol-2-yl]-phenyl}-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-piperidin-4-yl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(1-methyl-piperidin-4-yl)-1H-imidazol-2-yl]-phenyl}-3H-quinazolin-4-one;

2-{4-[1-(1-acetyl-piperidin-4-yl)-1H-imidazol-2-yl]-phenyl}-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-isopropyl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-cyclopropyl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-cyclobutyl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-cyclopentyl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(tetrahydro-furan-3-yl)-1H-imidazol-2-yl]-phenyl}-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-pyrrolidin-3-yl-1H-imidazol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(1-methyl-pyrrolidin-3-yl)-1H-imidazol-2-yl]-phenyl}-3H-quinazolin-4-one;

2-{4-[1-(1-acetyl-pyrrolidin-3-yl)-1H-imidazol-2-yl]-phenyl}-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(1-methanesulfonyl-pyrrolidin-3-yl)-1H-imidazol-2-yl]-phenyl}-3H-quinazolin-4-one;

N-[2-(2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-imidazol-1-yl)-ethyl]-acetamide;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-hydroxy-ethyl)-1H-imidazol-2-yl]-phenyl}-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-methoxy-ethyl)-1H-imidazol-2-yl]-phenyl}-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-methoxy-1-methyl-ethyl)-1H-imidazol-2-yl]-phenyl}-3H-quinazolin-4-one;

2-(2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-imidazol-1-yl)-acetamide;

2-(2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-imidazol-1-yl)-N-methyl-acetamide;

2-[4-(5-amino-furan-2-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

2-[4-(5-aminomethyl-furan-2-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

5-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-furan-2-carboxylic acid amide;

2-{4-[5-(1-amino-1-methyl-ethyl)-furan-2-yl]-phenyl}-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

2-[4-(3-amino-furan-2-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(3-dimethylaminomethyl-furan-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[3-(1-dimethylamino-1-methyl-ethyl)-furan-2-yl]-phenyl}-3H-quinazolin-4-one;

2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-furan-3-carboxylic acid amide;

3-(5-chloro-pyridin-2-yl)-2-(4-oxazol-2-yl-phenyl)-3H-quinazolin-4-one;

2-[4-(5-aminomethyl-oxazol-2-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-oxazole-5-carboxylic acid amide;

2-[4-(4-aminomethyl-oxazol-2-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-oxazole-4-carboxylic acid amide;

3-(5-chloro-pyridin-2-yl)-2-(4-thiazol-2-yl-phenyl)-3H-quinazolin-4-one;

2-[4-(5-aminomethyl-thiazol-2-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-thiazole-5-carboxylic acid amide;

2-[4-(4-amino-thiazol-2-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

N-(2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-thiazol-4-yl)-acetamide;

2-[4-(5-amino-thiazol-2-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

N-(2-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-thiazol-5-yl)-acetamide;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-imidazolidin-1-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-[1,3]diazepan-1-yl)-phenyl]-3H-quinazolin-4-one;

2-[4-(3-amino-2-oxo-piperidin-1-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(3-dimethylamino-2-oxo-piperidin-1-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-3-pyrrolidin-1-yl-piperidin-1-yl)-phenyl]-3H-quinazolin-4-one;

N-(1-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-2-oxo-piperidin-3-yl)-acetamide;

2-[4-(3-amino-2-oxo-pyrrolidin-1-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-dimethylaminomethyl-imidazol-1-yl)-phenyl]-3H-quinazolin-4-one;

1-{4-[3-(5-chloro-pyridin-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-phenyl}-1H-imidazole-2-carboxylic acid dimethylamide;

3-(5-chloro-pyridin-2-yl)-2-(4-isoxazol-5-yl-phenyl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-(4-oxazol-5-yl-phenyl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-(4-thiazol-5-yl-phenyl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(3H-[1,2,3]triazol-4-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(5-methyl-4H-[1,2,4]triazol-3-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(5-methyl-[1,3,4]thiadiazol-2-yl)-phenyl]-3H-quinazolin-4-one;

2-biphenyl-4-yl-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

2-(2'-amino-biphenyl-4-yl)-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-(2'-dimethylamino-biphenyl-4-yl)-3H-quinazolin-4-one;

2-(2'-aminomethyl-biphenyl-4-yl)-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-(2'-dimethylaminomethyl-biphenyl-4-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-(4-pyridin-2-yl-phenyl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-(4-pyridin-3-yl-phenyl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-(4-pyridin-4-yl-phenyl)-3H-quinazolin-4-one;

2-[4-(2-amino-pyridin-3-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

2-[4-(2-aminomethyl-pyridin-3-yl)-phenyl]-3-(5-chloro-pyridin-2-yl)-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-dimethylaminomethyl-pyridin-3-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-3H-quinazolin-4-one;

6-chloro-3-(5-chloro-pyridin-2-yl)-2-[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-6-fluoro-2-[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-3H-quinazolin-4-one;

6-bromo-3-(5-chloro-pyridin-2-yl)-2-[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-4-oxo-3,4-dihydro-quinazoline-6-carbonitrile;

3-(5-chloro-pyridin-2-yl)-2-[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-6-methoxy-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[2-fluoro-4-(2-oxo-piperidin-1-yl)-phenyl]-4-oxo-3,4-dihydro-quinazoline-6-carboxylic acid amide;

6-chloro-3-(5-chloro-pyridin-2-yl)-2-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-6-methoxy-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-6-fluoro-2-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-4-oxo-3,4-dihydro-quinazoline-6-carbonitrile;

3-(4-chloro-phenyl)-2-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-3H-quinazolin-4-one;

2-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-3-(4-methoxy-phenyl)-3H-quinazolin-4-one;

3-(3-chloro-phenyl)-2-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-3H-quinazolin-4-one;

2-fluoro-5-{2-[2-fluoro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]-4-oxo-4H-quinazolin-3-yl}-benzonitrile;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-pyrrolidin-1-yl)-phenyl]-3H-quinazolin-4-one;

3-(4-chloro-phenyl)-2-[4-(1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(4-methoxy-phenyl)-2-[4-(1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(3-chloro-phenyl)-2-[4-(1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(3-chloro-phenyl)-2-[4-(1-methyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(4-chloro-phenyl)-2-[4-(1-methyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-6-methoxy-2-[4-(1-methyl-1H-pyrrol-2-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-dimethylamino-ethyl)-1H-pyrrol-2-yl]-phenyl}-6-methoxy-3H-quinazolin-4-one;

6-chloro-3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-dimethylamino-ethyl)-1H-pyrrol-2-yl]-phenyl}-3H-quinazolin-4-one;

6-chloro-3-(4-chloro-phenyl)-2-{4-[1-(2-dimethylamino-ethyl)-1H-pyrrol-2-yl]-phenyl}-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-6-methoxy-2-[4-(2-oxo-imidazolidin-1-yl)-phenyl]-3H-quinazolin-4-one;

6-chloro-3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-imidazolidin-1-yl)-phenyl]-3H-quinazolin-4-one;

6-chloro-3-(4-chloro-phenyl)-2-[4-(2-oxo-imidazolidin-1-yl)-phenyl]-3H-quinazolin-4-one;

6-chloro-3-(4-methoxy-phenyl)-2-[4-(2-oxo-imidazolidin-1-yl)-phenyl]-3H-quinazolin-4-one;

6-chloro-3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-6-methoxy-2-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-dimethylaminomethyl-4,5-dihydro-imidazol-1-yl)-phenyl]-6-methoxy-3H-quinazolin-4-one;

3-(4-chloro-phenyl)-2-[4-(2-dimethylaminomethyl-4,5-dihydro-imidazol-1-yl)-phenyl]-6-methoxy-3H-quinazolin-4-one;

6-chloro-3-(4-chloro-phenyl)-2-[4-(2-dimethylaminomethyl-4,5-dihydro-imidazol-1-yl)-phenyl]-3H-quinazolin-4-one;

6-bromo-3-(4-chloro-phenyl)-2-[4-(2-dimethylaminomethyl-4,5-dihydro-imidazol-1-yl)-phenyl]-3H-quinazolin-4-one;

2-[4-(2-dimethylaminomethyl-4,5-dihydro-imidazol-1-yl)-phenyl]-3-(4-methoxy-phenyl)-6-methyl-3H-quinazolin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1H-pyrrol-2-yl)-phenyl]-3H-pyrido[3,2-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-methyl-1H-pyrrol-2-yl)-phenyl]-3H-pyrido[3,2-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-methylamino-ethyl)-1H-pyrrol-2-yl]-phenyl}-3H-pyrido[3,2-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1H-pyrrol-2-yl)-phenyl]-3H-pyrido[4,3-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-methyl-1H-pyrrol-2-yl)-phenyl]-3H-pyrido[4,3-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1H-pyrrol-2-yl)-phenyl]-3H-pyrido[3,4-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1H-pyrrol-2-yl)-phenyl]-3H-thieno[3,4-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1H-imidazol-2-yl)-phenyl]-3H-pyrido[3,2-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1H-imidazol-2-yl)-phenyl]-3H-thieno[3,4-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(1-methyl-1H-imidazol-2-yl)-phenyl]-3H-thieno[3,4-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-3H-pyrido[3,2-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-3H-pyrido[4,3-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-3H-pyrido[3,4-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-3H-thieno[3,4-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-imidazolidin-1-yl)-phenyl]-3H-pyrido[3,2-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-imidazolidin-1-yl)-phenyl]-3H-pyrido[4,3-d]pyrimidin-4-one;

6-(5-chloro-pyridin-2-yl)-5-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-6H-[1,2,5]oxadiazolo[3,4-d]pyrimidin-7-one;

6-(5-chloro-pyridin-2-yl)-5-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-6H-isoxazolo[4,3-d]pyrimidin-7-one;

6-(5-chloro-pyridin-2-yl)-5-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-6H-thiazolo[5,4-d]pyrimidin-7-one;

1-(5-chloro-pyridin-2-yl)-7-methyl-2-[4-(2-oxo-tetrahydro-pyrimidin-1-yl)-phenyl]-1,7-dihydro-purin-6-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(2-oxo-imidazolidin-1-yl)-phenyl]-3H-thieno[3,2-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-5-methyl-2-[4-(2-oxo-imidazolidin-1-yl)-phenyl]-3,5-dihydro-pyrrolo[3,2-d]pyrimidin-4-one;

6-(5-chloro-pyridin-2-yl)-1-methyl-5-[4-(2-oxo-imidazolidin-1-yl)-phenyl]-1,6-dihydro-pyrazolo[4,3-d]pyrimidin-7-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(3-dimethylamino-2-oxo-piperidin-1-yl)-phenyl]-3H-furo[3,2-d]pyrimidin-4-one;

3-(5-chloro-pyridin-2-yl)-2-[4-(3-dimethylamino-2-oxo-piperidin-1-yl)-phenyl]-5-methyl-3,5-dihydro-pyrrolo[3,2-d]pyrimidin-4-one; and,

6-(5-chloro-pyridin-2-yl)-5-[4-(3-dimethylamino-2-oxo-piperidin-1-yl)-phenyl]-1-methyl-1,6-dihydro-pyrazolo[4,3-d]pyrimidin-7-one;

or a pharmaceutically acceptable salt form thereof.

[00159] In another embodiment, the present invention provides novel pharmaceutical compositions, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

[00160] In another embodiment, the present invention provides a novel method for treating a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

[00161] In another preferred embodiment, the present invention provides a novel method, wherein the thromboembolic disorder is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart.

[00162] In another preferred embodiment, the present invention provides a novel method, wherein the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling

catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, or (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis.

[00163] In another embodiment, the present invention provides a novel method of treating a patient in need of thromboembolic disorder treatment, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a thromboembolic disorder

[00164] In another embodiment, the present invention provides a novel method, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a thromboembolic disorder.

[00165] In another embodiment, the present invention provides a novel method for treating a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a first and second therapeutic agent, wherein the first therapeutic agent is compound of the present invention or a pharmaceutically acceptable salt thereof and the second therapeutic agent is at least one agent selected from a second factor Xa inhibitor, an anti-coagulant agent, an anti-platelet agent, a thrombin inhibiting agent, a thrombolytic agent, and a fibrinolytic agent.

[00166] In another preferred embodiment, the present invention provides a novel method, wherein the second therapeutic agent is at least one agent selected from warfarin, unfractionated heparin, low molecular weight heparin, synthetic pentasaccharide, hirudin, argatrobanas, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, melagatran, disulfatohirudin, tissue plasminogen activator, modified tissue plasminogen activator, anistreplase, urokinase, and streptokinase.

[00167] In another preferred embodiment, the present invention provides a novel method, wherein the second therapeutic agent is at least one anti-platelet agent.

[00168] In another preferred embodiment, the present invention provides a novel method, wherein the anti-platelet agent is aspirin and clopidogrel.

[00169] In another preferred embodiment, the present invention provides a novel method, wherein the anti-platelet agent is clopidogrel.

[00170] In another embodiment, the present invention provides a novel article of manufacture, comprising:

(a) a first container;

(b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and,

(c) a package insert stating that the pharmaceutical composition can be used for the treatment of a thromboembolic disorder.

[00171] In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising:

(d) a second container;

wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

[00172] In another embodiment, the present invention provides a novel article of manufacture, comprising:

(a) a first container;

(b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and,

(c) a package insert stating that the pharmaceutical composition can be used in combination with a second therapeutic agent to treat a thromboembolic disorder.

[00173] In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising:

(d) a second container;

wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

[00174] In another embodiment, the present invention provides a compound of the present invention for use in therapy.

[00175] In another embodiment, the present invention provides the use of a compound of the present invention as described above for the manufacture of a medicament for the treatment of a thromboembolic disorder.

[00176] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional more preferred embodiments. It is also to be understood that each individual element of the preferred embodiments is its own independent preferred embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

DEFINITIONS

[00177] The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. All tautomers of shown or described compounds are also considered to be part of the present invention.

[00178] Preferably, the molecular weight of compounds of the present invention is less than about 500, 550, 600, 650, 700, 750, or 800 grams per mole. Preferably, the molecular weight is less than about 800 grams per mole. More

preferably, the molecular weight is less than about 750 grams per mole. Even more preferably, the molecular weight is less than about 700 grams per mole.

[00179] The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N). The present invention, in general, does not cover groups such as N-halo, S(O)H, and SO_2H.

[00180] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

[00181] When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[00182] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[00183] In cases wherein there are amines on the compounds of this invention, these can be converted to amine N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of this invention.

Thus, all shown and claimed amines are considered to cover both the shown amine and its N-oxide (N→O) derivative.

[00184] As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C_{1-6} alkyl, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-6} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-7} cycloalkyl is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Alkenyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more unsaturated carbon-carbon bonds that may occur in any stable point along the chain, such as ethenyl and propenyl. C_{2-6} alkenyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. "Alkynyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more triple carbon-carbon bonds that may occur in any stable point along the chain, such as ethynyl and propynyl. C_{2-6} Alkynyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups.

[00185] "Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

[00186] As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, or unsaturated (aromatic). Examples of such carbocycles include, but are

not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. As shown above, bridged rings are also included in the definition of carbocycle (e.g., [2.2.2]bicyclooctane). A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a trycyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[00187] As used herein, the term "heterocycle" or "heterocyclic group" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 ring heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_p$). The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heterotams independently selected from the group consisting of N, O and S. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_p$). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not

more than 1. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Preferred bridges include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a trycyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[00188] Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[00189] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of

human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00190] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic.

[00191] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p 1445, the disclosure of which is hereby incorporated by reference.

[00192] Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are

intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

[00193] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that there presently recited compounds do not contain a N-halo, $S(O)_2H$, or S(O)H group.

[00194] "Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

[00195] As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting it development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

[00196] "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit factor Xa. "Therapeutically effective amount" is also intended to include an amount of the combination of compounds claimed that is effective to inhibit factor Xa. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme*

Regul. **1984**, *22*:27-55, occurs when the effect (in this case, inhibition of factor Xa) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antithrombotic effect, or some other beneficial effect of the combination compared with the individual components.

SYNTHESIS

[00197] The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

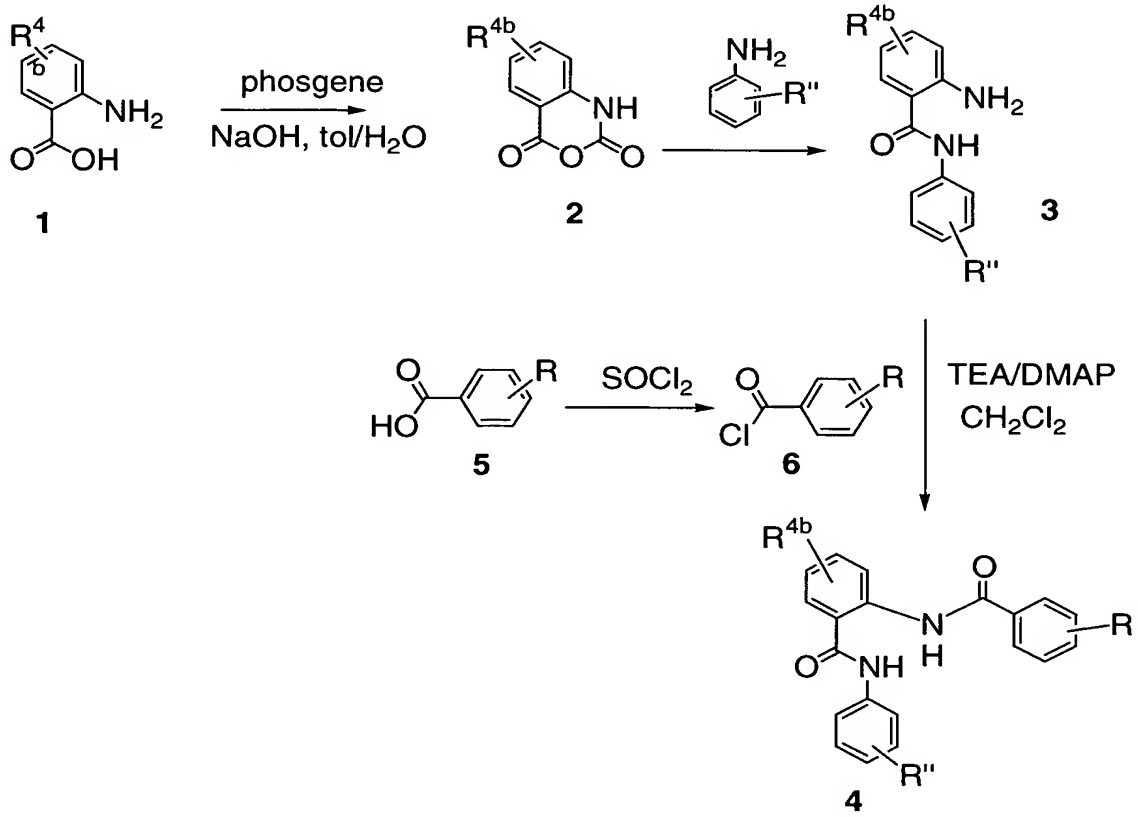
[00198] It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1991). All references cited herein are hereby incorporated in their entirety herein by reference.

[00199] Synthesis of compounds of the present invention involving intermediate **4** is accomplished via standard methods known to those skilled in the art. This general route is outlined in Schemes 1-5.

[00200] Construction of compounds with general structure **4** can be performed starting with **1** as shown in Scheme 1. Anhydride **2** can be obtained by treatment of **1**

with phosgene in basic condition. Intermediate **3** can be obtained by ring opening of **2**, and intermediate **4** can be formed via amide bond formation.

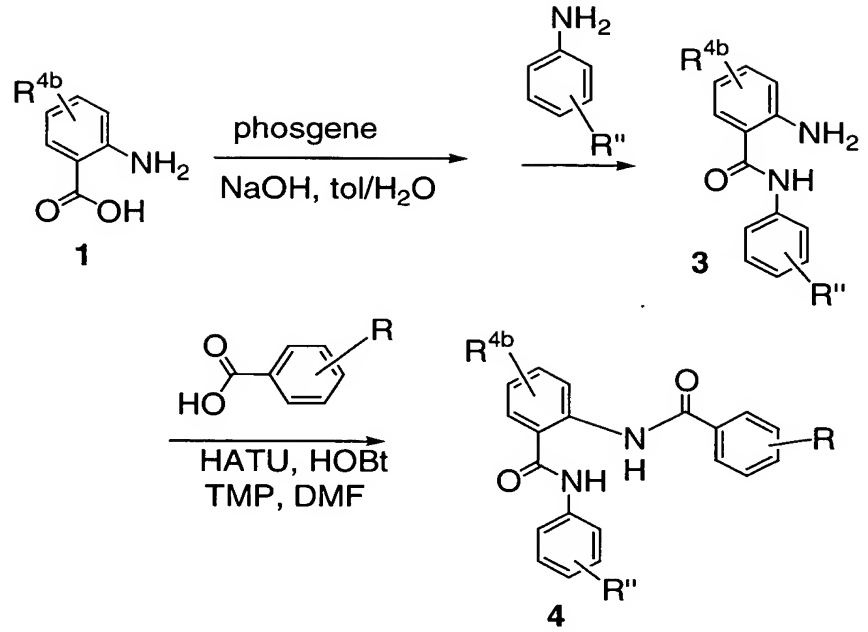
Scheme 1



[00201] During the synthesis of these compounds, protecting groups to prevent cross-reaction during the reaction conditions optionally protect the functional groups of the substituents. Examples of suitable protecting groups and their uses are described in "The Peptides: Analysis, Synthesis, Biology", academic press, Vol. 3 (Groii. Et. Al. Eds., 1981). Functional group transformations and coupling reactions that can be used to prepare compounds of the present invention are described in "Advanced Organic Chemistry: Reaction, Mechanism, and Structure" (March, et. Al., fourth Ed.) and "Comprehensive Organic Transformations" (Larock, sencond Ed.).

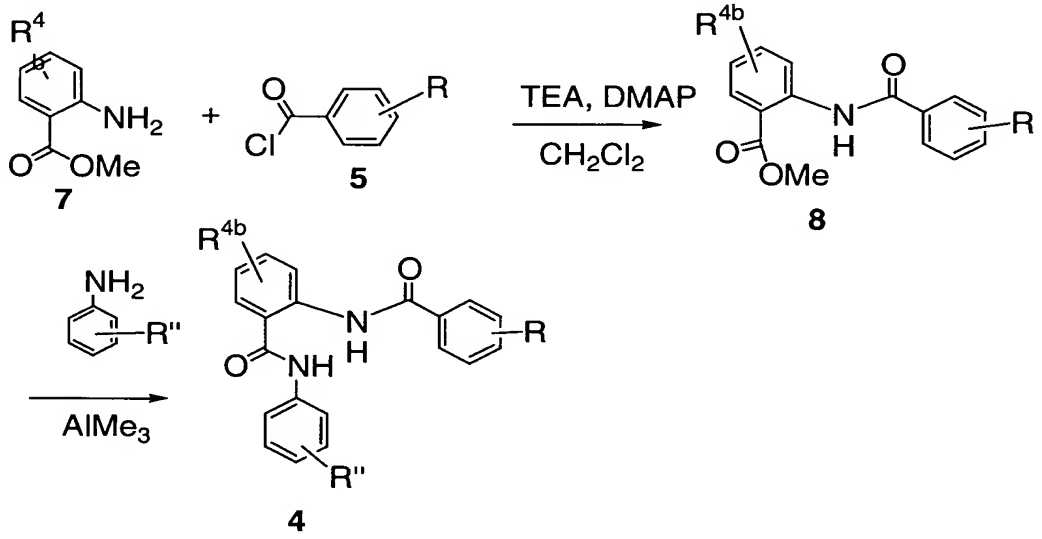
[00202] Alternatively, intermediate **4** can be obtained via peptide coupling conditions from **3** as shown in Scheme 2.

Scheme 2



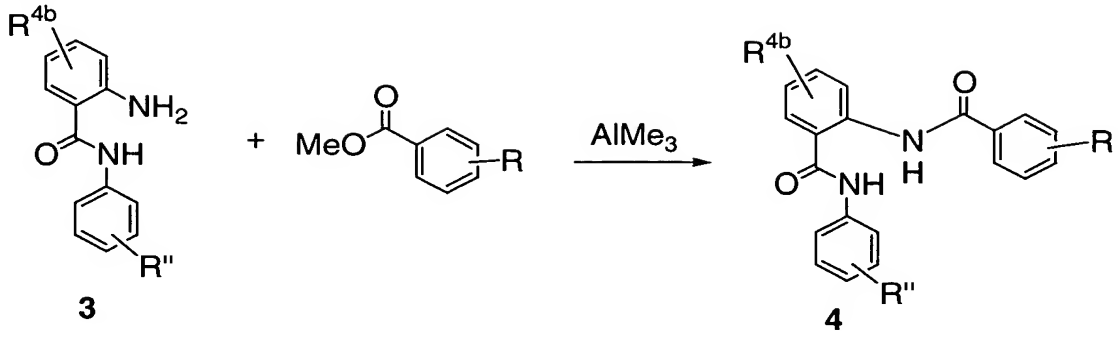
[00203] Alternatively, intermediate **4** can be obtained via the Weinreb reaction (Organic Synthesis, Vol. 59, 49) as described in Scheme 3.

Scheme 3



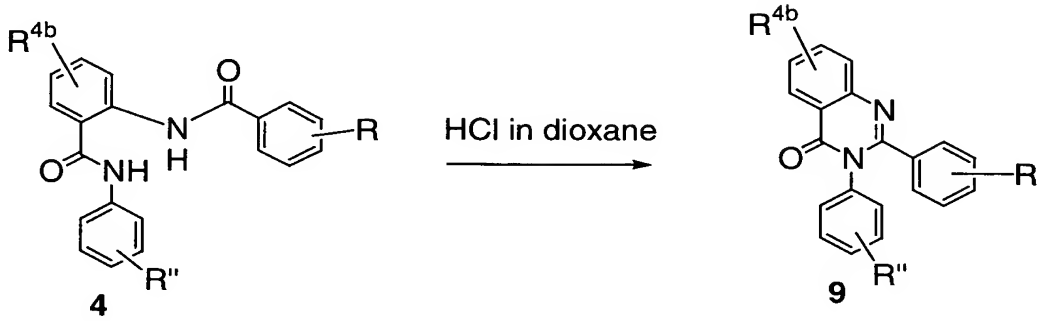
[00204] Alternatively, intermediate **4** can be obtained via Weinreb reaction where **3** has an aniline functionality as described in Scheme 4.

Scheme 4



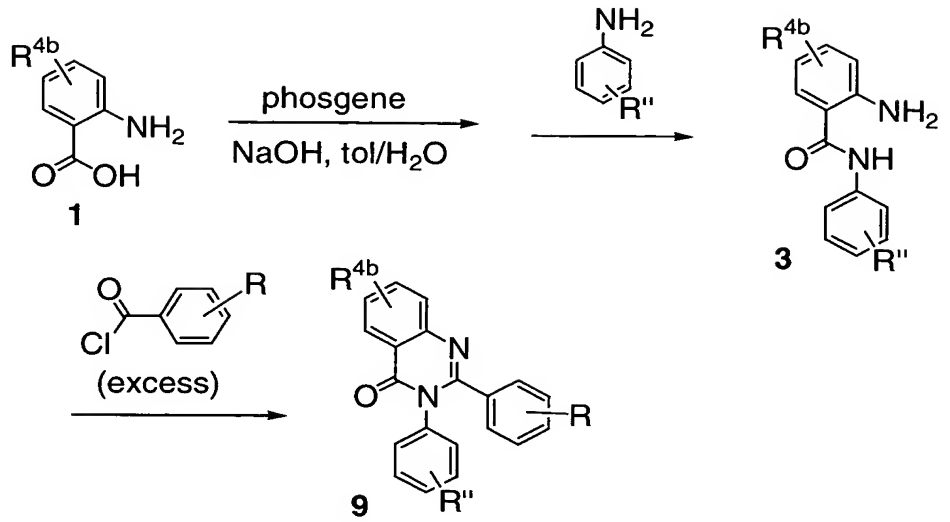
[00205] Compounds of the present invention can be obtained from **4** via acidic cyclization as described in Scheme 5.

Scheme 5



[00206] Alternatively, compounds of the present invention can be obtained from intermediate **3** in the presence of excess of acid chloride and base like triethylamine as shown in Scheme 6.

Scheme 6



[00207] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

UTILITY

[00208] The compounds of this invention are inhibitors of factor Xa and are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals (i.e., factor Xa-associated disorders). In general, a thromboembolic disorder is a circulatory disease caused by blood clots (i.e., diseases involving fibrin formation, platelet activation, and/or platelet aggregation). The term "thromboembolic disorders" as used herein includes arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart. The term "thromboembolic disorders" as used herein also includes specific disorders selected from, but not limited to, unstable angina or other acute coronary syndromes, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary

embolism, and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, or (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis. It is noted that thrombosis includes occlusion (e.g. after a bypass) and reocclusion (e.g., during or after percutaneous transluminal coronary angioplasty). The thromboembolic disorders may result from conditions including but not limited to atherosclerosis, surgery or surgical complications, prolonged immobilization, arterial fibrillation, congenital thrombophilia, cancer, diabetes, effects of medications or hormones, and complications of pregnancy. The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.

[00209] The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Diapharma/Chromogenix, West Chester, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nM. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i.

[00210] Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5% PEG 8000. The Michaelis constant, K_m, for substrate hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate K_i values:

$$(v_o - v_s)/v_s = I/(K_i\ (1 + S/K_m))$$

where:

v_o is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;

I is the concentration of inhibitor;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate;

K_m is the Michaelis constant.

[00211] Compounds tested in the above assay are considered to be active if they exhibit a K_i of $\leq$10 μM. Preferred compounds of the present invention have K_i's of $\leq$1 μM. More preferred compounds of the present invention have K_i's of $\leq$0.1 μM. Even more preferred compounds of the present invention have K_i's of $\leq$0.01 μM. Still more preferred compounds of the present invention have K_i's of $\leq$0.001 μM. Using the methodology described above, a number of compounds of the present invention were found to exhibit K_i's of $\leq$10 μM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

[00212] The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing that contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After forty minutes, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group. The ID_{50} values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

[00213] The compounds of the present invention may also be useful as inhibitors of serine proteases, notably human thrombin, Factor VIIa, Factor IXa, Factor XIa, urokinase, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the

treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

[00214] Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990), herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, was incubated with various substrate concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm that arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of the reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a K_i of less than 10 μm, thereby confirming the utility of the compounds of the present invention as effective thrombin inhibitors.

[00215] The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

[00216] The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of the present invention that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

[00217] By "administered in combination" or "combination therapy" it is meant that a compound of the present invention and one or more additional therapeutic

agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin (either unfractionated heparin or any commercially available low molecular weight heparin), synthetic pentasaccharide, direct acting thrombin inhibitors including hirudin and argatrobanas well as other factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

[00218] The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function, for example by inhibiting the aggregation, adhesion or granular secretion of platelets. Agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam, and pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA) and piroxicam are preferred. Other suitable platelet inhibitory agents include IIb/IIIa antagonists (e.g., tirofiban, eptifibatide, and abciximab), thromboxane-A2-receptor antagonists (e.g., ifetroban), thromboxane-A2-synthetase inhibitors, PDE-III inhibitors (e.g., dipyridamole), and pharmaceutically acceptable salts or prodrugs thereof.

[00219] The term anti-platelet agents (or platelet inhibitory agents), as used herein, is also intended to include ADP (adenosine diphosphate) receptor antagonists, preferably antagonists of the purinergic receptors P_2Y_1 and P_2Y_{12}, with P_2Y_{12} being even more preferred. Preferred P_2Y_{12} receptor antagonists include ticlopidine and clopidogrel, including pharmaceutically acceptable salts or prodrugs thereof. Clopidogrel is an even more preferred agent. Ticlopidine and clopidogrel are also preferred compounds since they are known to be gentle on the gastro-intestinal tract in use.

[00220] The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various

thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boropeptides, heparins, hirudin, argatroban, and melagatran, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal α-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. The term thrombolytics or fibrinolytic agents (or thrombolytics or fibrinolytics), as used herein, denote agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator (natural or recombinant) and modified forms thereof, anistreplase, urokinase, streptokinase, tenecteplase (TNK), lanoteplase (nPA), factor VIIa inhibitors, PAI-1 inhibitors (i.e., inactivators of tissue plasminogen activator inhibitors), alpha2-antiplasmin inhibitors, and anisoylated plasminogen streptokinase activator complex, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in EP 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

[00222] Examples of suitable anti-arrythmic agents for use in combination with the present compounds include: Class I agents (such as propafenone); Class II agents (such as carvadiol and propranolol); Class III agents (such as sotalol, dofetilide, amiodarone, azimilide and ibutilide); Class IV agents (such as ditiazem and verapamil); K^+ channel openers such as I_{Ach} inhibitors, and I_{Kur} inhibitors (e.g., compounds such as those disclosed in WO01/40231).

[00223] Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include: alpha adrenergic blockers; beta

adrenergic blockers; calcium channel blockers (e.g., diltiazem, verapamil, nifedipine, amlodipine and mybefradil); diruetics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone); renin inhibitors; ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril); AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan); ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265); Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389); neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat, gemopatrilat and nitrates).

[00224] Examples of suitable calcium channel blockers (L-type or T-type) for use in combination with the compounds of the present invention include diltiazem, verapamil, nifedipine, amlodipine and mybefradil.

[00225] Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

[00226] Examples of suitable diruetics for use in combination with the compounds of the present invention include: chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, and spironolactone.

[00227] Examples of suitable mineralocorticoid receptor antagonists for use in combination with the compounds of the present invention include sprionolactone and eplirinone.

[00228] Examples of suitable phospodiesterase inhibitors for use in combination with the compounds of the present invention include: PDE III inhibitors (such as cilostazol); and PDE V inhibitors (such as sildenafil).

[00229] Examples of suitable cholesterol/lipid lowering agents and lipid profile therapies for use in combination with the compounds of the present invention include: HMG-CoA reductase inhibitors (e.g., pravastatin, lovastatin, atorvastatin, simvastatin, fluvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522

(a.k.a. rosuvastatin, or atavastatin or visastatin)); squalene synthetase inhibitors; fibrates; bile acid sequestrants (such as questran); ACAT inhibitors; MTP inhibitors; lipooxygenase inhibitors; choesterol absorption inhibitors; and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

[00230] Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include: biguanides (e.g., metformin); glucosidase inhibitors (e.g., acarbose); insulins (including insulin secretagogues or insulin sensitizers); meglitinides (e.g., repaglinide); sulfonylureas (e.g., glimepiride, glyburide and glipizide); biguanide/glyburide combinations (e.g., glucovance), thiozolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in WO00/59506, glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

[00231] Examples of suitable anti-depressant agents for use in combination with the compounds of the present invention include nefazodone and sertraline.

[00232] Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include: prednisone; dexamethasone; enbrel; protien tyrosine kinase (PTK) inhibitors; cyclooxygenase inhibitors (including NSAIDs, and COX-1 and/or COX-2 inhibitors); aspirin; indomethacin; ibuprofen; prioxicam; naproxen; celecoxib; and/or rofecoxib.

[00233] Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate and raloxifene.

[00234] Examples of suitable hormone replacement therapies for use in combination with the compounds of the present invention include estrogen (e.g., congugated estrogens) and estradiol.

[00235] Examples of suitable anti-coagulants for use in combination with the compounds of the present invention include heparins (e.g., unfractioned and low molecular weight heparins such as enoxaparin and dalteparin).

[00236] Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include orlistat and aP2 inhibitors (such as those disclosed in WO00/59506).

[00237] Examples of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, and hydroxyzine pamoate.

[00238] Examples of suitable anti-proliferative agents for use in combination with the compounds of the present invention include cyclosporin A, paclitaxel, adriamycin; epithilones, cisplatin, and carboplatin.

[00239] Examples of suitable anti-ulcer and gastroesophageal reflux disease agents for use in combination with the compounds of the present invention include famotidine, ranitidine, and omeprazole.

[00240] Administration of the compounds of the present invention (i.e., a first therapeutic agent) in combination with at least one additional therapeutic agent (i.e., a second therapeutic agent), preferably affords an efficacy advantage over the compounds and agents alone, preferably while permitting the use of lower doses of each (i.e., a synergistic combination). A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety. It is preferred that at least one of the therapeutic agents is administered in a sub-therapeutic dose. It is even more preferred that all of the therapeutic agents be administered in sub-therapeutic doses. Sub-therapeutic is intended to mean an amount of a therapeutic agent that by itself does not give the desired therapeutic effect for the condition or disease being treated. Synergistic combination is intended to mean that the observed effect of the combination is greater than the sum of the individual agents administered alone.

[00241] The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

[00242] The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown

sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude factor Xa was present.

[00243] The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment of a thromboembolic disorder (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent to treat a thromboembolic disorder. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

[00244] The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube (e.g., for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

[00245] The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (e.g., cardboard or plastic), crates, cartons, bags (e.g., paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is

preferable that the package insert is physically attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

[00246] The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (e.g., the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (e.g., paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (e.g., printed or applied).

DOSAGE AND FORMULATION

[00247] The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[00248] The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

[00249] By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

[00250] Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[00251] The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

[00252] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

[00253] The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[00254] Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

[00255] Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

[00256] Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[00257] Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[00258] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing

agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl-or propyl-paraben, and chlorobutanol.

[00259] Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, a standard reference text in this field.

[00260] Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

[00261] Where the compounds of the present invention are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

[00262] Where the compounds of Formula I are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

[00263] Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

[00264] Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but ratheR is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

[00265] These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

[00266] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are afforded for illustration of the invention and are not intended to be limiting thereof.

Example 1

2-Biphenyl-4-yl-6-chloro-3-(5-chloro-pyridine-2-yl)-3*H*-quinazolin-4-one

Step a:

[00267] To a solution of 2-amino-4-chloropyridine (129 mg, 1.0 mmol) in anhydrous THF at –78°C was added KHMDS (4.0 mL, 0.5 M solution in toluene). The mixture was stirred at this temperature under N_2 for 30 min. and a solution of 5-chloro-isatoic anhydride (198.0 mg, 1.0 mmol) in THF was added to the above mixture. The resulting mixture was warmed to room temperature gradually and stirred for 10 h. The reaction mixture was quenched with sat'd NH_4Cl solution, most of the solvent was evaporated, and the residue was diluted with ethyl acetate, washed with brine, and dried over $MgSO_4$. Removal of solvent and chromatography on silica gel (20% ethyl acetate in hexane) yielded the desired 2-amino-5-chloro-N-(5-chloro-pyridin-2-yl)-benzamide as light brown solid. MS found: $(M+1)^+ = 282.2$.

Step b:

[00268] To a solution of biphenyl-4-carboxylic acid (198 mg, 1.0 mmol) in CH_2Cl_2 and DMF (0.5 mL) was added oxalyl chloride (2.0 mmol). The mixture was stirred for 2 hr under N_2. Solvent was removed and the residue was dried on vacuum to give the desired acid chloride.

[00269] To a mixture of the product obtained from Step a (124 mg, 0.44 mmol), TEA (0.25 mL), and DAMP (11.0 mg) in CH_2Cl_2 was added a solution of the above acid chloride in CH_2Cl_2 at 0°C. The mixture was warmed to room temperature and stirred over night under N_2. The mixture was washed with water and purified with reverse phase HPLC (20% CH_3CN/H_2O, 40 mL/min) to provide the desired biphenyl-4-carboxylic acid [4-chloro-2-(-chloropyridin-2-ylcarbamoyl)-phenyl]-amide as white solid. MS found: $(M+1)^+ = 462.2$.

Step c:

[00270] A solution of the product obtained from above (25.0 mg, 0.054 mmol) in 5 mL of 4N HCl in dioxane and 1.0 mL of THF was refluxed for 6 hr. The mixture was cooled to room temperature and purified with reverse phase HPLC (10% CH_3CN in H_2O, 20 mL/min) to give the desired product as white solid. MS found: $(M+1)^+ = 444.0$.

Example 2

6-Chloro-3-(5-chloro-pyridine)-2-(4-methoxy-phenyl)-3*H*-quinazolin-4-one

[00271] Following a procedure analogous to that described in Example 1, 6-chloro-3-(5-chloro-pyridine)-2-(4-methoxy-phenyl)-3*H*-quinazolin-4-one was obtained as white solid. MS found: $(M+1)^+ = 398.0$.

[00272] Numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise that as specifically described herein.